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Terlipressin versus adrenaline in an infant animal model of asphyxial cardiac arrest

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Abstract Purpose: The objective of this study was to compare the efficacy of terlipressin versus adrenaline in an experimental infant animal model of asphyxial cardiac arrest (ACA). **Design:** Prospective randomised animal study.

Setting: Laboratory research department of a university hospital. **Methods:** Seventy-one, 2-month-old, mechanically ventilated piglets were investigated. ACA was induced by removal of mechanical ventilation. Resuscitation was performed by means of manual external chest compressions and mechanical ventilation (CC + V). After 3 min of CC + V, return of spontaneous circulation (ROSC) was observed in 11 animals. The 60 piglets without ROSC were then randomised to the four study groups: adrenaline standard dose (Asd): 0.01 mg/kg/3 min; adrenaline high dose (Ahd): first dose (0.01 mg/kg) and subsequent doses (0.1 mg/kg/3 min); terlipressin (T): 20 µg/kg/6 min; and adrenaline standard dose plus terlipressin (Asd + T). **Measurements and results:** The relationship between haemodynamic

(heart rate, blood pressure, ECG rhythm, cardiac index), respiratory (end-tidal CO₂, blood gas analysis) and tissue perfusion (gastric intramucosal pH, central, cerebral and renal saturation) parameters and ROSC was analysed. ROSC was achieved in three piglets treated with Asd (20%), four treated with Ahd (26.7%), one treated with T (6.7%) and seven treated with Asd + T (46.7%) ($P = 0.099$). ROSC was achieved in 43.1% of animals with pulseless electrical activity, 30.4% with asystole and none with ventricular fibrillation ($P = 0.0001$).

Conclusion: In this infant animal model of cardiac arrest, there was a non-significant trend towards better outcome when terlipressin was combined with adrenaline compared with the use of adrenaline or terlipressin alone.

Keywords Cardiac arrest · Adrenaline · Terlipressin · Cardiopulmonary resuscitation · Paediatrics

Introduction

Adrenaline is the recommended drug for the treatment of cardiac arrest (CA) both in children and adults based on its vasoconstrictive and inotropic effects [1]. Although many efforts have been made to improve the results of

resuscitation, the prognosis in children who suffer cardiac arrest remains poor [2–6].

Vasopressin and terlipressin, a synthetic vasopressin analogue with a longer half-life, produce vasoconstriction by the stimulation of V1 receptors [7]. Several studies have shown that vasopressin increases vital organ blood

flow and cerebral oxygen delivery; in addition, adrenaline plus vasopressin achieved a higher return of spontaneous circulation (ROSC) and neurological recovery when compared to adrenaline alone in adult animals with CA secondary to ventricular fibrillation (VF) [8–11].

Initial clinical studies with vasopressin plus adrenaline were not found to improve the results in adult patients with ventricular fibrillation and pulseless electrical activity (PEA) compared to adrenaline alone, but there was an improvement in the results of resuscitation in cases of asystole and refractory CA [12, 13]. However, a recent trial found that the administration of vasopressin plus adrenaline did not improve the resuscitation outcome in adult out-of-hospital CA irrespective of the electrocardiographic rhythm [14].

Cardiac arrest in children has different clinical and epidemiological characteristics compared to adults: more frequent respiratory origin and CA secondary to hypoxia rather than primary CA, and more frequent asystole and PEA than ventricular fibrillation (VF) as the initial arrest rhythm [3, 4].

Very few studies have analysed the efficacy of vasopressin or terlipressin in an infant animal model of cardiac arrest [15]. In the paediatric clinical setting, only limited case series reporting the use of vasopressin or terlipressin as a last resort have been published [16–18].

The objective of this investigation was to compare the efficacy of adrenaline, terlipressin and the combination of the two drugs in an experimental animal model of infant asphyxial CA.

Methods

International guidelines for the care of experimental animals were applied throughout the study; the experimental protocol was approved by the Gregorio Marañón's Institutional Ethical Animal Investigation Committee. Seventy-one healthy 2-to-3-month-old Maryland pigs with a mean weight of 9.1 (2.2) kg were used.

Initial anaesthesia was performed with intramuscular ketamine and atropine, followed by propofol, fentanyl and atracurium for oral endotracheal intubation.

The animals were ventilated using a mechanical ventilator (Dräger SA2, Babylog N, Lubeck, Germany) with a respiratory rate of 20 breaths/min, tidal volume of 10 ml/kg, FiO_2 of 50% and PEEP of 3 cmH₂O. Ventilation was adjusted to achieve an expired CO_2 (EtCO_2) between 33 and 35 mmHg and a PaCO_2 between 35 and 45 mmHg.

Sedation and muscle relaxation (propofol 10 mg/kg/h, fentanyl 10 mg/kg/h and atracurium 2 mg/kg/h by continuous infusion) were maintained throughout the procedure, inhibiting the presence of spontaneous respiration. Monitoring included ECG, peripheral oxygen saturation (Visconnet[®] monitor, KGB, Madrid, Spain),

cerebral and renal saturation by near infrared spectroscopy (INVOS[®] Cerebral Oximeter monitor, Somanetics, Troy, MI), and the respiratory volumes and pressures, FiO_2 , EtCO_2 , by means of a spirometer connected to the endotracheal tube and an S5[®] monitor (Datex Ohmeda, Madison, WI). A 4-F PiCCO[®] catheter was inserted into the femoral artery to measure the blood pressure and cardiac output by means of a femoral arterial thermodilution system (PiCCO[®], Pulsion Medical Systems, Munich, Germany), a 5F catheter was inserted through the external jugular vein to measure the central venous pressure (CVP), a 5.5F Swan-Ganz catheter [Vigilance[®] (Edwards Lifesciences, Irvine, CA)] was inserted via the femoral vein to monitor the pulmonary arterial pressure, and a 4-F catheter was inserted in the jugular bulb vein to measure jugular venous oxygen saturation (SjvO_2). To measure gastric intramucosal pH, a 7-F tonometric catheter (TRIP, Tonometrics Division, Instrumentarium Corp, Helsinki, Finland) was passed into the stomach and connected to a S5[®] Monitor (Datex-Ohmeda, Madison, WI).

Blood gases were analysed using the GEM Premier 3000[®] blood gas analyser (Instrumentation Laboratory, Lexington, KY), and standard full blood counts and measurement of aspartate aminotransferase, alanine aminotransferase and troponin were performed.

After baseline data had been collected, cardiac arrest was induced by disconnection from the respirator for at least 10 min. Resuscitation was started only when CA (defined as a heart rate less than 60 beats/min and systolic arterial pressure less than 30 mmHg) was confirmed and after at least 10 min of disconnection. Initial resuscitation (CC + V) was performed by means of manual external chest compressions (100 compressions/min) and mechanical ventilation (20 breaths/min with 100% oxygen). After 3 min of CC + V, vital data were collected, and return of spontaneous circulation (ROSC) was checked. The animals without ROSC were then randomly distributed into four study groups: adrenaline standard dose (Asd): 0.01 mg/kg/3 min; adrenaline high dose (Ahd): first standard dose (0.01 mg/kg) followed by subsequent "high doses" (0.1 mg/kg/3 min); terlipressin (T): 20 mcg/kg/6 min; adrenaline standard and terlipressin (Asd + T). In this last group, the first doses of adrenaline and terlipressin were given together; subsequent doses of adrenaline were given every 3 min and terlipressin every 6 min. In all cases, bicarbonate was administered after 9 and 18 min of resuscitation. Pigs in ventricular fibrillation were defibrillated during resuscitation.

Resuscitation was stopped when ROSC was achieved or after 20 min. After ROSC, mechanical ventilation was maintained with 100% oxygen and adjusted to obtain an arterial PCO_2 between 35 and 45 mmHg (4.7–6 kPa).

The following parameters were recorded at baseline and every 3 min during resuscitation: inspiratory tidal volume, EtCO_2 , systolic, diastolic and mean arterial pressure (MAP), CVP, mean pulmonary arterial pressure

(mPAP), peripheral haemoglobin saturation, and cerebral and renal haemoglobin saturation. Cardiac index (CI) measurement was performed simultaneously by means of pulmonary and arterial thermodilution. Arterial, venous and jugular bulb blood gases and lactate were also determined every 5 min. Haemodynamic and laboratory data were collected at 5, 15 and 30 min after ROSC.

On completion of the experiment, all successfully resuscitated animals were killed by the administration of sedative overdose and the intravenous injection of potassium chloride.

The statistical analysis was performed using the SPSS (version 16.0) statistical package. Pearson's chi-squared test was used for qualitative variables analysis, and Fisher's exact test when *n* was less than 20 or when any value was less than 5. Student's *t* test was used to compare quantitative variables between independent groups and the Mann-Whitney *U* test for variables with a non-normal distribution. Analysis of variance for repeated measurements (ANOVA) was used to study the changes in the parameters over the course of the experiment. Logistic regression was performed to assess the influence of factors on the ROSC. A *P* value less than 0.05 was considered significant.

Results

A total of 71 animals were included in the study. ROSC was achieved with CC + V in 11 animals, and the

remaining 60 were randomised to the four therapeutic groups. The study groups did not differ with respect to age, weight and baseline haemodynamic and laboratory parameters (Table 1). There were no significant differences between groups with regard to haemodynamic, respiratory and perfusion parameters, and blood gas profiles at the time of disconnection from the respirator (Table 1) or 10 min after disconnection (Table 2), though at that time there was a trend towards a lower PaCO₂ in the animals that achieved ROSC with only CC + V. The mean time from disconnection of mechanical ventilation to cardiac arrest was 10.0 (3.3) min, and this did not differ between groups [ROSC without drugs: 10.3 (3.2) min; Asd: 10.8 (3.7) min; Ahd: 9.8 (3.5) min; T: 9.3 (2.3) min; Asd + T: 9.9 (3.8) min].

At the beginning of resuscitation, 23 animals (32.4%) were in asystole, 44 (62%) presented pulseless electrical activity with bradycardia and 4 (5.6%) ventricular fibrillation. There were no differences between groups (Table 3).

The outcomes after CA and resuscitation are shown in Fig. 1. Twenty-six animals (36.6%) achieved ROSC in 4.9 (2.8) min (range 1–12 min). ROSC was achieved within the first 6 min of resuscitation in 20 of these 26 animals (76.9%). Eleven animals (15.5%) achieved ROSC with chest compressions and ventilation only within the first 3 min of CC + V. Fifteen (25%) of the other 60 animals treated with CC + V plus medication achieved ROSC (Fig. 1). When the four therapeutic groups were compared, there was a trend towards a higher

Table 1 Haemodynamic and laboratory data at baseline

Group	Total	CC + V	Adrenaline standard dose	Adrenaline high dose	Terlipressin	Adrenaline standard dose + Terlipressin	<i>P</i>
Number of animals	71	11	15	15	15	15	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Weight (kg)	9.1 (2.2)	8.7 (1.3)	9.7 (3.7)	9.1 (2.0)	9.2 (1.8)	8.6 (1.4)	0.822
HR (bpm)	119 (22)	116 (18)	113 (23)	121 (23)	126 (22)	119 (27)	0.542
MAP (mmHg)	90 (18)	96 (18)	93 (23)	90 (22)	90 (14)	89 (12)	0.875
CVP (mmHg)	7 (3)	7 (4)	8 (3)	7 (3)	8 (3)	8 (2)	0.445
CI (l/min/m ²)	5.7 (1.5)	5.2 (1.1)	4.6 (0.8)	6.8 (2.2)	5.4 (0.9)	6.0 (1.6)	0.106
pHi	7.21 (0.13)	7.30 (0.09)	7.23 (0.14)	7.20 (0.14)	7.24 (0.08)	7.15 (0.15)	0.268
Cerebral oxygenation (%)	59 (11)	58 (3)	60 (16)	60 (13)	58 (10)	59 (10)	0.928
Renal oxygenation (%)	60 (5)	58 (7)	56 (3)	62 (2)	60 (4)	64 (6)	0.094
Troponine (ng/ml)	0.02 (0.03)	0.04 (0.06)	0.02 (0.01)	0.02 (0.03)	0.02 (0.01)	0.03 (0.04)	0.670
pHa	7.39 (0.08)	7.38 (0.08)	7.41 (0.08)	7.37 (0.07)	7.40 (0.07)	7.43 (0.11)	0.369
PaCO ₂ (mmHg)	40 (7)	38 (7)	39 (6)	42 (5)	40 (8)	39 (7)	0.612
PaO ₂ (mmHg)	169 (67)	157 (58)	141 (63)	168 (57)	205 (55)	176 (94)	0.080
SaO ₂ (%)	98 (10)	99 (1)	99 (2)	98 (2)	99 (1)	100 (0.4)	0.306
BE arterial	0.3 (5.4)	-1.3 (4.7)	0.6 (5.7)	-0.2 (5.6)	0.6 (4.5)	1.7 (6.4)	0.500
Lactate (mmol/l)	0.8 (0.4)	0.6 (0.2)	1.0 (0.5)	0.8 (0.4)	0.8 (0.4)	0.8 (0.5)	0.592
SvO ₂ (%)	78 (14)	84 (17)	71 (16)	78 (12)	79 (11)	78 (13)	0.088
SyO ₂ (%)	69 (14)	60 (22)	66 (12)	72 (19)	76 (6)	65 (13)	0.589
Satc O ₂ (%)	99 (1)	100 (0.5)	99 (2)	99 (1)	100 (0.5)	98 (1)	0.464
EtCO ₂ (mmHg)	35 (5)	32 (6)	35 (6)	38 (5)	37 (4)	33 (6)	0.336

HR Heart rate (bpm), MAP mean arterial pressure (mmHg), CVP central venous pressure (mmHg), CI cardiac index (l/min/m²), pHi gastric intramucosal pH, cerebral oxygenation cerebral oxygenation

by near infrared spectroscopy (NIRS). Renal oxygenation renal oxygenation by NIRS. a Arterial, v venous, y venous jugular bulb, Satc O₂ transcutaneous oxygen saturation, EtCO₂ end tidal CO₂

Table 2 Data 10 min after disconnection from the respirator

Group	Global	CC + V	Adrenaline standard dose	Adrenaline high dose	Terlipressin	Adrenaline standard dose + Terlipressin	<i>P</i>
Number of animals	71	11	15	15	15	15	0.215
Number of animals in cardiac arrest	57 (80%) Mean (SD)	8 (73%) Mean (SD)	10 (67%) Mean (SD)	12 (80%) Mean (SD)	14 (93%) Mean (SD)	13 (87%) Mean (SD)	
HR (bpm)	53 (42)	48 (46)	53 (45)	41 (50)	43 (25)	67 (45)	0.435
MAP (mmHg)	17 (27)	24 (23)	15 (29)	9 (12)	9 (15)	15 (28)	0.272
CVP (mmHg)	12 (7)	10 (7)	12 (5)	10 (10)	16 (6)	11 (5)	0.284
pHi	7.00 (0.18)	7.02 (0.09)	7.07 (0.13)	6.98 (0.28)	6.97 (0.26)	6.96 (0.14)	0.762
Cerebral oxygenation (%)	28 (13)	20 (7)	35 (20)	24 (14)	27 (5)	30 (11)	0.456
Renal oxygenation (%)	36 (8)	32 (3)	34 (10)	38 (7)	36 (7)	40 (7)	0.403
pHa	7.09 (0.08)	7.13 (0.07)	7.05 (0.10)	7.09 (0.08)	7.10 (0.08)	7.09 (0.09)	0.693
PaCO ₂ (mmHg)	77 (19)	58 (19)	89 (15)	79 (15)	73 (23)	81 (15)	0.074
PaO ₂ (mmHg)	18 (15)	15 (9)	27 (21)	23 (19)	10 (11)	14 (7)	0.314
SaO ₂ (%)	16 (16)	21 (7)	20 (19)	17 (19)	11 (15)	13 (12)	0.516
BEa	-6.9 (4.2)	-8.3 (6.2)	-6.1 (4.0)	-8.2 (3.7)	-7.4 (4.0)	-5.0 (3.2)	0.254
Lactate (mmol/l)	5.1 (2.1)	3.7 (2.4)	5.3 (2.8)	5.8 (1.6)	4.9 (1.8)	5.0 (2.0)	0.819
SvO ₂ (%)	17 (15)	13 (14)	30 (26)	20 (15)	10 (5)	14 (8)	0.343
BEv	-6.5 (5.3)	-7.5 (5.6)	-5 (4.6)	-9.6 (7.0)	-6.1 (1.8)	-4.4 (5.2)	0.436
pHy	7.11 (0.77)	Not measured	7.06 (0.11)	7.12 (0.08)	7.16 (0.08)	7.08 (0.06)	0.273
SyO ₂ (%)	24 (3)	Not measured	10 (11)	15 (7)	17 (13)	23 (15)	0.588

Comparison between groups

Fourteen animals were not yet in cardiac arrest at this moment. CI, Satc O₂ and EtCO₂ were not measured at this time

HR Heart rate (bpm), MAP mean arterial pressure (mmHg), CVP central venous pressure (mmHg), CI cardiac index (l/min/m²), pHi

gastric intramucosal pH, cerebral oxygenation cerebral oxygenation by near infrared spectroscopy (NIRS), renal oxygenation renal oxygenation by NIRS, a arterial, v venous, y venous jugular bulb, Satc O₂ transcutaneous oxygen saturation, EtCO₂: end tidal CO₂

Table 3 Electrocardiographic rhythm at the time of cardiac arrest

Group	Global	CC + V	Adrenaline standard dose	Adrenaline high dose	Terlipressin	Adrenaline standard dose + Terlipressin
Asystole	23 (32%)	4	5	7	3	4
PEA	44 (62%)	7	9	8	11	9
Ventricular fibrillation	4 (6%)	0	1	0	1	2
Total	71	11	15	15	15	15

P = 0.672

PEA pulseless electrical activity

frequency of ROSC in the Asd + T group (*P* = 0.099). A calculation was performed to determine the sample size needed to show statistical differences with this incidence rate: 76 animals would be needed (19 in each group) to achieve a significance of *P* = 0.031. When the four groups were compared by pairs, ROSC in the Asd + T group (46.7%) was significantly higher than in the T group (6.7%) (*P* < 0.05). No significant differences were observed between the other pairs.

The time to achieve ROSC was similar in all groups. In the Asd group, the three animals that attained ROSC needed only one dose of adrenaline. In the Ahd group, two animals needed two doses of adrenaline and an additional two animals needed three doses. In the T group, ROSC was achieved with only one dose of terlipressin in the one piglet in which ROSC occurred, and in the Asd + T group, six animals needed one dose of adrenaline and terlipressin, and one needed two doses of

adrenaline and one dose of terlipressin. In all therapeutic groups, ROSC was achieved within the first 12 min of resuscitation.

The small proportion of animals that achieved ROSC in the therapeutic groups precludes any meaningful statistical comparison of the measured parameters. We therefore only analysed the relationship between ROSC and the haemodynamic/perfusion parameters and laboratory data before disconnection from the mechanical ventilation and during cardiac arrest. Five minutes after disconnection from the respirator there were no differences in any of the haemodynamic, respiratory or perfusion parameters between animals with and without ROSC. At 10 min, the systolic and mean arterial pressures were higher in the pigs that eventually achieved ROSC (Table 4). PaCO₂ was also lower in the pigs that achieved ROSC than in the other animals (Table 4). ROSC was achieved in 43.1% of pigs with PEA and

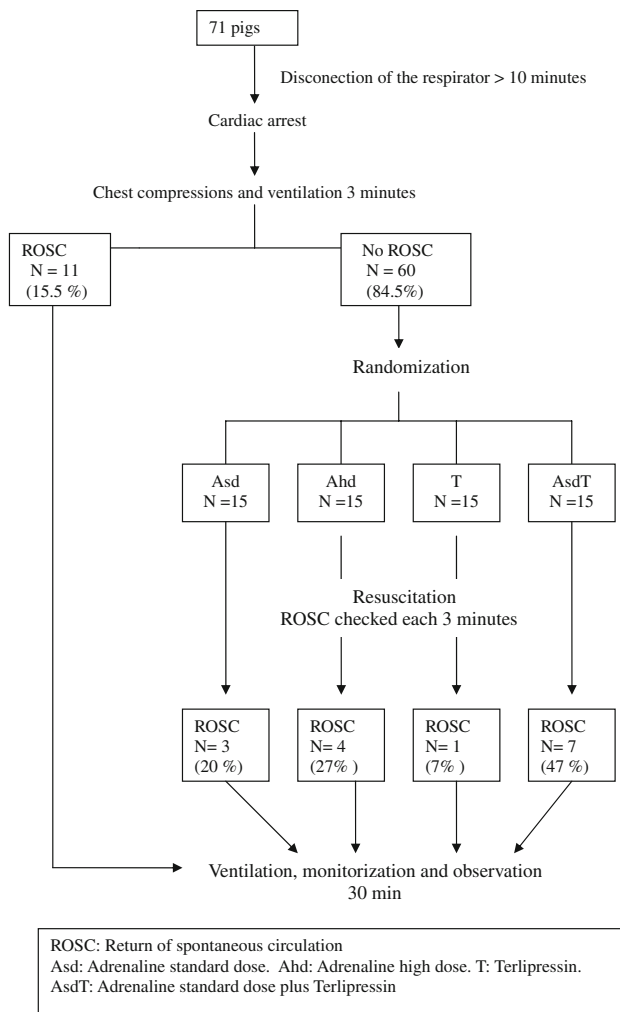


Fig. 1 Utstein style template for recording the outcome of the animals

30.4% of those with asystole, but in none of the four pigs with ventricular fibrillation ($P = 0.0001$). The frequency of ROSC in cases of asystole was similar to ROSC with PEA ($P = 0.309$). No other haemodynamic, respiratory or organ perfusion parameters or laboratory data were related to ROSC at any time (Table 4). These factors were included in a multivariate stepwise logistic regression model to study the predictive power of each one on ROSC (Table 5).

Discussion

This is the first experimental study that has compared the effects of adrenaline at standard and high doses, terlipressin alone and the association of adrenaline at standard dose plus terlipressin in a model specifically designed to

simulate the most common situation in paediatric cardiac arrest (asphyxial and/or hypoxic).

In this infant model, our results indicate that there was a non-significant trend towards a better outcome when terlipressin was combined with adrenaline compared with adrenaline or terlipressin used alone.

These results agree with the findings of other authors performing animal studies designed to simulate the conditions of cardiac arrest in adult patients (non-asphyxial/hypoxic) [9, 10, 19].

However, clinical studies in adults have yielded discordant results, possibly due to the different time from arrest to the initiation of resuscitation and drug administration (immediate in experimental designs and very variable but much longer in real life) [20]. It is well known that time to first drug administration is a predictor of ROSC [21]. To avoid this bias we have programmed a CA preceded by asphyxia of at least 10-min duration, which meant a time from the onset of asphyxia to drug administration of at least 13 min. The ROSC rate with this protocol was low, but was similar to figures reported in recent studies of out-of-hospital cardiac arrest in children; this indicates that our model truly resembles the usual clinical conditions where the study drugs will eventually be administered.

In our study no outcome differences were found between standard and high doses of adrenaline, agreeing with previous clinical studies in children [22, 23]. However, our protocol was not designed to explore the potential short, intermediate and long-term deleterious effects of high doses of adrenaline, and no conclusion can therefore be made in this regard.

On the other hand, there is a notably low rate of ROSC achieved in the group of animals treated with terlipressin alone. These data agree with those published by Voekel [15] when exploring the effects of vasopressin also in an infant animal model and suggest that terlipressin and vasopressin are potent vasopressors but cannot substitute adrenaline in the pharmacological treatment of asphyxial cardiac arrest. However, the association of adrenaline and terlipressin/vasopressin could have a role in cardiopulmonary resuscitation, and the additive effect of the drugs could be explained by their agonistic effects on different and specific receptors. This hypothesis is supported by a recent preliminary study in adults that found the combination of corticosteroids, adrenaline and vasopressin to have a positive impact on survival [24].

Evaluation of the haemodynamic, respiratory, tissue perfusion and laboratory data 10 min after ventilator disconnection found the blood pressure to be higher and arterial PCO_2 lower in the animals that ultimately achieved ROSC than in those with resuscitation failure. Several studies have demonstrated that the presence of gasping during cardiorespiratory arrest and CPR is associated with a better outcome, probably because it contributes to maintaining a minimum level of alveolar

Table 4 Comparison between animals with and without ROSC 10 min after disconnection from the ventilator

	ROSC		No ROSC		<i>P</i>
	Mean	SD	Mean	SD	
Weight (kg)	9	1.5	9	2.5	
Time from disconnection to CA (min)	10.4	3.5	10.4	3.5	
Data 10 min after disconnection from the ventilator					
HR (bpm)	50	37	51	47	1
MAP (mmHg)	21	24	10	20	0.021
CVP (mmHg)	11	5	13	8	0.478
pHi	6.97	0.18	7.02	0.18	0.832
Cerebral oxygenation (%)	23	9	32	14	0.065
Renal oxygenation (%)	34	8	38	7	0.218
Troponin (ng/ml)	0.07	0.06	0.10	0.05	0.558
pHa	7.12	0.06	7.06	0.09	0.067
PaCO ₂ (mmHg)	67	16	83	19	0.005
PaO ₂ (mmHg)	15	11	20	18	0.431
SaO ₂ (%)	17	17	15	16	0.433
BEa	-6.3	4.5	-7.3	4.1	0.424
Lactate (mmol/l)	4.6	2.4	5.3	2.0	0.628
SvO ₂ (%)	14	11	20	19	0.455
SyO ₂ (%)	16	7	17	12	0.946
	Number of animals	%	Number of animals	%	
ECG in cardiac arrest					
Asystole	7	30	16	70	0.000
PEA	19	43	25	57	
Ventricular fibrillation	0	0	4	100	
Treatment					
Adrenaline standard dose	3	20	12	80	0.099
Adrenaline high dose	4	27	11	73	
Terlipressin	1	7	14	93	
Adrenaline plus terlipressin	7	7	8	53	

HR Heart rate (bpm), MAP mean arterial pressure (mmHg), CVP central venous pressure (mmHg), CI cardiac index (l/min/m²), pHi intramural gastric pH, cerebral oxygenation cerebral oxygenation

by near infrared spectroscopy (NIRS), renal oxygenation renal oxygenation by NIRS, a arterial, v venous, y venous jugular bulb Satc O₂ transcutaneous oxygen saturation, EtCO₂ end tidal CO₂

Table 5 Logistic regression study of predictive factors of ROSC

Factor	Odds ratio	95% CI	<i>P</i>
ECG rhythm at time of diagnosis of CRA	1.737	0.59–5.06	0.312
PaCO ₂ 10 min after ventilator disconnection	0.950	0.91–0.99	0.021
MAP 10 min after ventilator disconnection	1.024	0.99–1.05	0.091
Adrenaline + Terlipressin	1.704	0.53–5.41	0.366

CRA Cardiorespiratory arrest, MAP mean arterial pressure

ventilation [25]. None of our animals presented gasping because our protocol included muscle relaxation. Further studies are necessary to confirm the prognostic value of the PaCO₂ in paediatric cardiac arrest.

In our study, animals with PEA had a higher rate of ROSC than those with asystole or VF. However, there were only four animals with VF. There is little information about the prognosis of VF in infants and children [6, 26]; in some studies VF was found to be associated with a better prognosis than asystole or PEA [6], but other studies did not find this association [26]. Asphyxia is

followed by progressive hypoxic organ damage affecting not only the heart and brain, but also other organs. This damage seems to be very difficult to reverse and could explain the low ROSC rate observed in our study.

Our study has certain limitations. Although there were 71 animals overall, the number of animals in each group was insufficient to detect statistically significant differences. In addition, although we can state that ventilation was fully controlled by mechanical ventilation, the quality of the chest compressions could have been suboptimal. We performed manual cardiac massage as it is done in

clinical practice, measuring and controlling the frequency of compressions to adjust to 100/min. However, we did not control depth of compression or coronary blood flow, which are factors directly associated with ROSC.

In our sample, we did not find differences between groups (ROSC vs. no ROSC) when the measured parameters were compared. Theoretically, at least, animals treated with the combination of adrenaline and terlipressin should have increased vasoconstriction with a resultant increase in peripheral vascular resistance and fall in cardiac output and gastric intramucosal pH, which could compromise organ perfusion [27, 28]. It is possible that some of the differences would have reached significance with a larger number of animals.

To our knowledge, there are no previous experimental studies on the effects of terlipressin in cardiac arrest. Consequently, the optimal dose and dose interval have not been determined. Arbitrarily we decided to administer similar doses to those used in published studies in children with shock and cardiorespiratory arrest [17, 18, 29], that is, 20 µg/kg. Although terlipressin has a long half-life (4 h), the uncertainty about the correct dose meant we decided to repeat the dose every 6 min while ROSC was not achieved. Our results seem to confirm that additional doses are not needed during CPR because only one animal

needed a second dose. This may be one of the advantages of terlipressin, but additional studies are needed to determine whether its prolonged effects are exclusively beneficial or could cause ischaemic adverse effects in the post-resuscitation period.

In parallel with clinical results, most animals achieved ROSC during the initial minutes of resuscitation. It is well known that the probability of achieving ROSC falls exponentially with time [4]. Thus, if alternative/complementary vasoconstrictor drugs such as vasopressin or terlipressin are considered, they should be administered as soon as possible.

In conclusion, this infant animal model of cardiac arrest showed a non-significant trend towards a better outcome when terlipressin was combined with adrenaline compared with adrenaline or terlipressin used alone.

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