Effects of terlipressin and naloxone compared with epinephrine in a rat model of asphyxia-induced cardiac arrest

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OBJECTIVE: To evaluate the hemodynamic and metabolic effects of terlipressin and naloxone in cardiac arrest.

METHODS: Cardiac arrest in rats was induced by asphyxia and maintained for 3.5 minutes. Animals were then resuscitated and randomized into one of six groups: placebo (n = 7), epinephrine (0.02 mg/kg; n = 7), naloxone (1 mg/kg; n = 7) or terlipressin, of which three different doses were tested: 50 μg/kg (TP50; n = 7), 100 μg/kg (TP100; n = 7) and 150 μg/kg (TP150; n = 7). Hemodynamic variables were measured at baseline and at 10 (T10), 20 (T20), 30 (T30), 45 (T45) and 60 (T60) minutes after cardiac arrest. Arterial blood samples were collected at T10, T30 and T60.

RESULTS: The mean arterial pressure values in the TP50 group were higher than those in the epinephrine group at T10 (165 *vs*. 112 mmHg), T20 (160 *vs*. 82 mmHg), T30 (143 *vs*. 66 mmHg), T45 (119 *vs*. 67 mmHg) and T60 (96 *vs*. 66.8 mmHg). The blood lactate level was lower in the naloxone group than in the epinephrine group at T10 (5.15 *vs*. 10.5 mmol/L), T30 (2.57 *vs*. 5.24 mmol/L) and T60 (2.1 *vs*. 4.1 mmol/L).

CONCLUSIONS: In this rat model of asphyxia-induced cardiac arrest, terlipressin and naloxone were effective vasopressors in cardiopulmonary resuscitation and presented better metabolic profiles than epinephrine. Terlipressin provided better hemodynamic stability than epinephrine.

KEYWORDS: Cardiopulmonary Resuscitation; Cardiac Arrest; Naloxone; Lypressin/Analogs and Derivatives; Asphyxia.

■ INTRODUCTION

Survival rates and neurologic outcomes among patients who experience cardiac arrest (CA) are poor (1). Patients with an initial asystole rhythm have a worse prognosis than patients with ventricular fibrillation (VF) (2,3). Epinephrine is the recommended and most widely used vasopressor in this situation, although there is evidence that it increases oxygen consumption, reduces subendocardial perfusion (4) and causes severe myocardial dysfunction following the return of spontaneous circulation (ROSC) (5).

In addition, recent evidence suggests that epinephrine worsens perfusion in the cerebral microcirculation and increases the severity of cerebral ischemia during cardiopulmonary resuscitation (CPR) (6,7). In a previous study, the use

of epinephrine increased mortality in an experimental asphyxia-induced CA model (8). In the single published placebo-controlled human study, epinephrine increased the ROSC rate but was not better than a placebo with regard to neurological outcome or survival to discharge (9).

Two recent studies that used terlipressin to treat pediatric cardiac arrest (in a total of 12 children) produced encouraging results (10,11). However, terlipressin did not increase the rate of ROSC in two other recent experimental studies (12,13).

Studies that have used naloxone during CPR have produced conflicting results (14-24). The mechanism underlying the effect of naloxone during CPR remains unclear. One hypothesis is that hypoxia activates the endogenous opioid system, which is involved in the respiratory control system, stimulates catecholamine release and increases sympathetic nerve activity, thereby elevating heart rate and blood pressure (17). In addition, naloxone has possible anti-arrhythmic effects and ameliorates cardiac function, thereby most likely improving post-resuscitation myocardial dysfunction (21). Finally, naloxone has immunomodulatory effects and a possible protective role in postischemic heart injuries (21).

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Therefore, the current study was designed to evaluate the effects of terlipressin and naloxone in an experimental model of asphyxia-induced cardiac arrest in rats. The main hypothesis was that these drugs could provide better hemodynamic and/or metabolic profiles in the first hour post-CA than the standard treatment with epinephrine.

■ MATERIALS AND METHODS

This was a randomized, blinded, placebo-controlled experimental study that was approved by the Institutional Animal Investigation Committee and was conducted in accordance with the ARRIVE guidelines (Animals in Research: Reporting In Vivo Experiments) (25) and Utstein-style guidelines for uniform reporting of laboratory CPR research (26). The animals were managed in accordance with the Brazilian College of Animal Experimentation and National Institutes of Health Guidelines.

Animal preparation

Adult male Wistar rats with an average weight of 399 g (range: 340 to 445 g) were obtained from the Central Animal Laboratory of the School of Medicine and anesthetized with intraperitoneal injections of urethane (0.5 mg/kg) and ketamine (50 mg/kg). The proximal trachea was surgically dissected, and a 14-gauge cannula was inserted 10 mm into the trachea to the larynx. Mechanical ventilation was performed with a respiratory rate of 85 cycles/minute, tidal volume of 6 mL/kg, inspired oxygen fraction of 100% and positive end-expiratory pressure of 1 cm H_2O (Rodent Ventilator, model 683, Harvard Apparatus Inc., Natick, MA, USA). A catheter was inserted through the jugular vein and directed toward the right atrium to facilitate drug administration and volume replacement. For blood pressure measurement, the left femoral artery was cannulated, and a catheter was introduced. The catheters were connected to pressure transducers that were coupled to a calibrated preamplifier (Stemtech Inc., GPA-4 model 2, Menomonee Falls, WI, USA) and a computerized data acquisition system (DATAQ Instruments Inc., Akron, OH, USA). Systemic hemodynamic measurements were simultaneously recorded beat by beat. Measurements were taken at baseline and at the five following time points after CA: the 10th (T10), 20th (T20), 30th (T30), 45th (T45) and 60th (T60) minutes. Monitoring during the experiment included the following:

- Electrocardiogram: recorded continuously with two subcutaneous leads.
- Mean arterial pressure (MAP, mmHg).
- Temperature (rectal probe): temperature was maintained between 36 and 37℃ throughout the experiment using a passive external warming method (infrared lamp).

Vasopressors

The epinephrine dose was 0.02 mg/kg. Although some recent studies have used higher doses of epinephrine (0.04 to 0.05 mg/kg), doses higher than 0.03 mg/kg are associated with increased rates of myocardial dysfunction, neurological injury and a poor prognosis (27-29). The chosen naloxone dose was 1 mg/kg because lower doses have been associated with lower ROSC rates (15) and higher doses have not been demonstrated to be beneficial (19). The chosen terlipressin doses were extrapolated from pediatric

studies of CA (10,11). In these pediatric series (total of 12 patients), 10-20 µg/kg terlipressin was administered following the administration of a few doses of epinephrine. Therefore, when terlipressin was used alone, we chose higher doses (50, 100 and 150 µg/kg). All of the syringes were visually identical and contained 1 mL of fluid.

Asphyxia-induced cardiac arrest and resuscitation

A preparation and control phase of the experiment was performed to design a CA model (in anoxia) that had an ROSC rate of at least 50% with the placebo and approximately 100% with epinephrine. Several anoxia durations were studied (4 to 10 minutes). We observed that by defining a total anoxia time rather than a total CA time, the animals would be subjected to different CA durations. Therefore, our model characterized the exact time at which CA began; it measured the total time of arrest and not the total time of anoxia.

After the surgical preparation and hemodynamic stabilization of the animal, the trachea was obstructed to induce CA, which was defined as the loss of aortic pulsation and MAP <15 mmHg. After CA was confirmed, the animals were maintained in asphyxia for 3.5 additional minutes. Subsequently, the rats were resuscitated following standard procedures:

- Saline solution (SS) or one of the vasopressor drugs was administered (all in similar, standardized 1-mL syringes), which was followed by a flush of 0.5 mL of SS; both were given directly through a central venous catheter.
- Chest compressions (200/minute) were performed for all of the groups by a single researcher who was blinded to the administered vasopressor. The researcher was guided by an audio device (to ensure the correct compression frequency), and MAP was monitored and maintained at >30 mmHg.
- The animal was ventilated with 100% FiO_2; the respiratory rate was 70 cycles/min, and the tidal volume was 8 mL/kg.

ROSC was considered to have occurred when MAP remained >50 mmHg for a minimum of 5 consecutive minutes. Resuscitation efforts were discontinued in the absence of ROSC after 5 minutes of chest compressions.

A neuromuscular blockade was performed with pancuronium at 15 and 37 minutes after cardiac arrest. The dose was 0.5 mg/kg.

Arterial blood samples were collected at baseline and at T10, T30 and T60. Analyses were performed immediately after each collection and consisted of measurement of arterial blood gases (pH, pO_2, pCO_2, oxygen saturation, bicarbonate and base excess), sodium, potassium, hemoglobin, hematocrit, glucose and lactate. All of the examinations were performed using the same equipment (Radiometer ABL 835 Flex, Radiometer Medical ApS, Bronshoj, Denmark).

Statistical analysis

A database was created using Data Entry 4.0 software using the double-entry system. A statistical analysis was performed using PASW Statistics (18.0 for Macintosh). The qualitative data were expressed as frequencies and percentages, and the numerical data were described as mean

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Table 1 - Baseline variables of the different groups

Variable	Placebo (n = 7)	Epi (n = 7)	Nalo (n = 7)	TP50(n = 7)	TP100(n = 7)	TP150(n = 7)	p-value
Weight (g)	405±29	386±25	417±28	404±41	390±29	387±33	0.37
Heart rate	380±56	358±65	384±37	376±80	419±98	408±65	0.65
MAP (mm Hg)	106±10	120±17	110±14	108±13	121±16	106±11	0.16
Hb (g/dL)	16.4±0.7	16.2±0.5	16.3±0.9	16.7±0.7	16.8±0.7	15.9±0.9	0.23
Ht (%)	50.2±2.3	49.8±1.6	50±2.7	51±2.1	51±2.2	49±2.6	0.24
Na^+ (mmol/L)	139±2.6	137±1.8	138±2.6	137±2.2	139±3.2	137±1.7	0.33
K^+ (mmol/L)	3.9±0.2	4.0±0.3	4.3±0.3	4.2±0.2	4.1±0.4	4.3±0.5	0.43
Glucose (mg/dL)	208±30	222±40	212±20	212±29	216±38	207±31	0.93
paO_2 (torr)	343±83	316±80	298±54	338±68	367±60	294±94	0.42
$SatO_2$ (%)	97.8±0.2	97.7±0.3	97.7±0.1	97.7±0.5	97.7±0.2	97.4±0.5	0.79
pCO_2 (torr)	41±6.3	41±6.5	39±6.4	39±3.7	39±2.2	41±3.2	0.96
pH	7.36±0.04	7.36±0.04	7.38±0.05	7.36±0.03	7.38±0.03	7.37±0.06	0.94
Bic (mmol/L)	22.8±3.1	22.9±2.1	22.6±1.3	22.4±1.4	23.3±1.6	23.4±1.1	0.91
Base excess	−1.9±2.8	−1.6±1.8	−1.7±1.2	−2±1.5	−1.1±1.8	−.9±1	0.78
Lactate (mmol/L)	2.68±0.58	2.51±0.39	2.33±0.55	2.44±0.63	1.9±0.44	2.6±0.43	0.14

The values represent the mean ± SD.

values and standard deviations. The normal distribution of data was confirmed using the Kolmogorov-Smirnov test. To compare the mean values in the baseline variables, we used a one-way ANOVA. The ROSC analysis was performed using Fisher's exact test, and a post-hoc analysis was performed using the Bonferroni test. Two-tailed $p<0.05$ was considered significant.

RESULTS

The final sample consisted of 42 animals, which were randomized into one of the following groups: placebo (n = 7), epinephrine (EPI; n = 7), naloxone (Nalo; n = 7), terlipressin 50 μg/kg (TP50; n = 7), terlipressin 100 μg/kg (TP100; n = 7) or terlipressin 150 μg/kg (TP150; n = 7).

The groups were homogeneous, and there was no significant difference among them regarding hemodynamic and laboratory variables (Table 1). ROSC occurred in four of the seven animals (57%) in the placebo group and in 100% of the animals in the vasopressor groups (35 animals; $p = 0.002$). The time between the induction of anoxia and the onset of CA was 246.1 seconds (±67.4 sec), as shown in Table 2. The total time of hypoxia was not different between the groups and was calculated by adding the time between the onset of anoxia and CA to the time during which the animals remained in CA (3.5 min). During the first hour of the experiment, four animals died: two in the EPI group, one in the TP100 group and one in the TP150 group.

Mean arterial pressure and blood tests

The animals in the terlipressin groups had higher MAP values than animals in the epinephrine group (Table 3). However, the MAP levels were not significantly different when naloxone was compared with epinephrine.

The TP50 and naloxone groups had lower blood lactate values than the epinephrine group (Table 4). The best metabolic profile was observed in the naloxone group, and the worst profile was observed in the epinephrine group (Tables 5 and 6).

DISCUSSION

Our findings suggest that terlipressin and naloxone could be used as alternatives to epinephrine or vasopressin in the treatment of CA with a nonshockable rhythm (asystole/PEA). Terlipressin had a better hemodynamic metabolic profile than epinephrine. Naloxone was the vasopressor with the best metabolic profile.

In the present study, we chose three different terlipressin doses to evaluate their effects in resuscitation. The doses were compared both among themselves and with epinephrine and a placebo. This is the first study that aimed to study drugs (and dosages) of alternatives to epinephrine in the treatment of cardiac arrest.

In the context of asystole, our data suggest that very high doses (greater than or equal to 100 μg/kg) were associated with worse outcome and even worse metabolic profiles, perhaps because of the greater time necessary to obtain the ROSC. Moreover, 50 μg/kg terlipressin produced a more favorable profile than epinephrine in the first hour following ROSC. This favorable hemodynamic profile of terlipressin may be related to its increased vasopressor effect and its long duration of action (4 to 6 hours). Only two randomized studies have been published that used terlipressin as a vasopressor during CPR. Ovalle evaluated terlipressin in a pig model of ventricular fibrillation (13) and found that terlipressin did not differ from the placebo regarding effects on coronary perfusion pressure, and low rates of ROSC

Table 2 - Times (sec) between the onset of anoxia and cardiac arrest, time from cardiopulmonary resuscitation to the return of spontaneous circulation and the total time during which the animals remained in hypoxia

Variable	Placebo	Epi	Nalo	TP50	TP100	TP150	p-value
Onset of anoxia to CA	272±70	243±71	235±40	233±71	236±79	250±69	0.55
From CPR to ROSC	114±40[a]	79±43	86±27	110±57	125±59	142±77	0.16
Total hypoxia	482±70	453±71	445±40	443±71	446±79	460±69	0.55

The values represent the mean ± SD.
[a]Data from four animals (three animals did not present ROSC).

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Table 3 - Mean arterial pressure: comparisons of the groups *vs.* time

Groups	MAP (mmHg)				
	T10	T20	T30	T45	T60
Epi	112 ± 25	82 ± 25	66 ± 9	67 ± 12	66.8 ± 12
Nalo	138 ± 36	113 ± 24	97 ± 25	85 ± 24	86 ± 24
TP50	165 ± 18[a]	160 ± 7[b]	143 ± 10[b]	119 ± 19[b]	96 ± 16
TP100	156 ± 42	154 ± 11[b]	124 ± 18[b]	112 ± 8[a]	95 ± 9
TP150	170 ± 11[a]	155 ± 12[b]	149 ± 16[b]	120 ± 28[b]	101 ± 25
p-value[c]	0.016	0.000	0.000	0.003	0.088

a: $p < 0.05$ (compared with the epinephrine group).
b: $p < 0.01$ (compared with the epinephrine group).
c: ANOVA between groups.

were observed in both groups. As a monotherapy, perhaps the low dose of terlipressin (10 to 20 µg/kg) chosen explains these findings. In a pediatric model, ROSC was observed in three of 15 animals receiving standard doses of epinephrine, four of 15 animals receiving high-dose epinephrine, one of 15 animals receiving terlipressin and seven of 15 animals receiving both epinephrine and terlipressin (12). The differences between the groups were not significant. The use of propofol in a model of hypoxia-induced CA may not be desirable and may have contributed to the low frequency of ROSC in that study, which was much lower than the expected rates in pediatric CA models. Furthermore, a low dose of terlipressin (10 to 20 µg/kg) was chosen based on two pediatric series (10,11). The fact that the children in these studies had already received several epinephrine doses prior to receiving terlipressin may not have been considered when the dose of terlipressin was chosen as the only vasopressor in this model of CPR. Lower terlipressin doses have been shown to be effective in the treatment of septic shock (30-32). However, when used as a single drug in CA, higher doses of terlipressin may be necessary (>20 µg/kg). Our findings confirm that terlipressin is a fast-acting vasopressor whose initial effect is inherent and occurs before the endothelial conversion of terlipressin to lysine-vasopressin (33). In addition, we demonstrated that animals that received terlipressin maintained a significantly higher MAP than those that received epinephrine or vasopressin throughout the post-CA period.

No significant differences in MAP were observed with different doses of terlipressin. However, based on the values of lactate, bicarbonate and base excess, animals receiving a 50 µg/kg dose had a more favorable metabolic profile than those receiving 100 µg/kg or 150 µg/kg.

Table 4 - Blood lactate: comparisons of the groups *vs.* time

Groups	Blood lactate (mmol/L)		
	T10	T30	T60
Epi	10.5 ± 3.7	5.24 ± 3.2	4.1 ± 2.2
Nalo	5.15 ± 1.1[b]	2.57 ± 0.9[a]	2.1 ± 0.9[a]
TP50	6.6 ± 1.2[b]	2.57 ± 0.4[a]	2.05 ± 0.4[a]
TP100	6.7 ± 1.3[a]	3.88 ± 1.7	2.46 ± 0.3
TP150	7.34 ± 1.5	3.67 ± 0.6	2.84 ± 0.8
p-value*	0.0008	0.039	0.029

a: $p < 0.05$ (compared with the epinephrine group).
b: $p < 0.01$ (compared with the epinephrine group).
c: ANOVA between groups.

Table 5 - Base excess: comparisons of the groups *vs.* time

Groups	Base excess (mmol/L)		
	T10	T30	T60
Epi	-16.6 ± 3.5	-10.9 ± 5.2	-12 ± 7.4
Nalo	-9.7 ± 1.7[b]	-6.9 ± 2.9[a]	-6.7 ± 2.6
TP50	-11.8 ± 1.8[b]	-9 ± 1.8	-8.8 ± 1.9
TP100	-13.1 ± 1.5	-12.6 ± 2.1	-10.9 ± 1.5
TP150	-13.9 ± 1.7	-11.7 ± 1.2	-10.5 ± 2.2
p-value*	0.0001	0.0007	0.107

a: $p < 0.05$ (compared with the epinephrine group).
b: $p < 0.01$ (compared with the epinephrine group).
c: ANOVA between groups.

In other studies using naloxone in rat asphyxia models, the ROSC rates were similar to those obtained with epinephrine (seven of eight animals in each group) (16); there was a trend toward higher ROSC rates at a dose of 1 mg/kg compared with 0.5 mg/kg of naloxone (1 mg/kg: seven of eight animals; 0.5 mg/kg: three of eight animals) (15). In addition, the combination of epinephrine and naloxone decreased the time that was required to attain ROSC during CPR (naloxone plus epinephrine: 133 sec *vs.* epinephrine: 206 sec; $p < 0.01$) (23,24). However, it is difficult to interpret this evidence because of methodological problems in these studies. The international recommendations for research in CA (Utstein-style guidelines) were not followed, so it was not possible to assess similarities (or differences) between the animals regarding important baseline variables, and the animals were resuscitated without oxygen. Neither laboratory nor arterial blood gas values were monitored before, during or after CA. Finally, the epinephrine doses (0.04 to 0.05 mg/kg) were higher than the currently recommended doses.

In our study, all animals that were resuscitated with naloxone had ROSC and survived through the first hour following CA. The MAP curves in the rats receiving naloxone were intermediate between those in rats receiving terlipressin (better) and epinephrine (worse). Little is known about the possible benefits of naloxone in the treatment of CA. In the cardiovascular system, naloxone may increase sympathetic nervous system activity (34,35), which may increase heart rate and blood pressure. Naloxone could also act as an antiarrhythmic (36), and it could even attenuate myocardial dysfunction after CA (37). Our study is the first to show that naloxone has a favorable profile regarding bicarbonate, base excess and lactate levels when it is used as a vasopressor in CA. These results cannot be attributed to MAP and may instead be intrinsic to the vasopressor. Our

Table 6 - Bicarbonate: comparisons of the groups *vs.* time

Groups	Bicarbonate (mmol/L)		
	T10	T30	T60
Epi	8.1 ± 4.5	16.1 ± 3.6	14.7 ± 6.1
Nalo	18 ± 1.6[b]	19 ± 2.6[a]	19.2 ± 2.6
TP50	16.4 ± 1.7[a]	17.3 ± 1.9	16.9 ± 1.9
TP100	14.5 ± 1.1	14.2 ± 1.7	15.1 ± 1.3
TP150	14.3 ± 0.9	15.1 ± 1.1	16.4 ± 2.1
p-value*	0.017	0.006	0.152

a: $p < 0.05$ (compared with the epinephrine group).
b: $p < 0.01$ (compared with the epinephrine group).
c: ANOVA between groups.

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results are consistent with a previous finding that naloxone has a protective effect in ischemia by restoring mitochondrial activity and energy metabolism (38).

The strengths of our study include the fact that it was designed and performed with a uniform, reproducible sample and control of important variables associated with the prognosis of CA in asystole. Randomization produced homogeneous groups. The group allocation in this study was conducted in a blinded fashion. The measurement of the hemodynamic variables and blood tests were performed at several different intervals, both at baseline and during the experiment, which allowed a temporal analysis of the differences between the groups at different times (not only at a single time point). Resuscitation was performed using a standardized method, which included strict control of MAP levels during chest compressions. We defined the exact time that the animal remained without circulation (3.5 min). Therefore, this model can be used to study different stages of CA, and it allows investigators to adjust the time without effective circulation according to the intended research goals.

Despite these encouraging results, it is important to analyze these data with caution. The study was not designed to show any differences in the rates of ROSC between epinephrine and other drugs. Such an analysis may require a larger sample and a longer absence of circulation. The experiment evaluated a specific duration of CA, and the results could be different in protocols with longer-lasting CA. Furthermore, anesthesia with both ketamine and urethane can potentially interfere in epinephrine metabolism, thereby causing hemodynamic variations that may have affected the results. It is also possible that other agents, such benzodiazepines, etomidate and barbiturates, could have less interference. Nevertheless, most published studies have used ketamine and urethane. Finally, it is known that studies that are performed during CPR maneuvers in animals are often not confirmed in clinical trials.

This is the first study that aimed to study terlipressin in different dosages as an alternative to epinephrine in the treatment of cardiac arrest. Based on these results, new studies will be developed to compare the effects of terlipressin (50 μg/kg) and epinephrine in a pig model of cardiac arrest. Furthermore, lower doses of naloxone in association with terlipressin or epinephrine will be evaluated.

In this hypoxia-induced rat CA model, terlipressin and naloxone were effective vasopressors in resuscitation and produced better metabolic profiles than epinephrine. Terlipressin administration resulted in significantly better hemodynamic stability in the first hour following CA compared with epinephrine. Among the vasopressors that were studied in this experiment, naloxone had the best metabolic profile.

■ AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the study and supported the data and conclusions. Martins HS reviewed the literature, formulated the experiment, discussed the findings with a statistician, performed data analysis with a statistical professional and wrote the paper. Koike MK reviewed the literature, co-formulated the experiment, conducted the experiment (surgery) and revised the paper. Velasco IT managed the overall experiment, developed the methodology of the study, co-discussed the findings with a statistician and revised the paper.

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