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Experimental Cardiac Arrest Treatment with Adrenaline, Vasopressin, or Placebo

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Abstract

Background: The effect of vasoconstrictors in prolonged cardiopulmonary resuscitation (CPR) has not been fully clarified.

Objectives: To evaluate adrenaline and vasopressin pressure effect, and observe the return of spontaneous circulation (ROSC).

Methods: A prospective, randomized, blinded, and placebo-controlled study. After seven minutes of untreated ventricular fibrillation, pigs received two minutes cycles of CPR. Defibrillation was attempted (4 J/kg) once at 9 minutes, and after every cycle if a shockable rhythm was present, after what CPR was immediately resumed. At 9 minutes and every five minutes intervals, 0.02 mg/kg (n = 12 pigs) adrenaline, or 0.4 U/kg (n = 12) vasopressin, or 0.2 mL/kg (n = 8) 0.9% saline solution was administered. CPR continued for 30 minutes or until the ROSC.

Results: Coronary perfusion pressure increased to about 20 mmHg in the three groups. Following vasoconstrictors doses, pressure level reached 35 mmHg *versus* 15 mmHg with placebo (p < 0.001). Vasopressin effect remained at 15-20 mmHg after three doses *versus* zero with adrenaline or placebo. ROSC rate differed (p = 0.031) among adrenaline (10/12), vasopressin (6/12), and placebo (2/8). Time-to-ROSC did not differ (16 minutes), nor the number of doses previously received (one or two). There was no difference between vasoconstrictors, but against placebo, only adrenaline significantly increased the ROSC rate (p = 0.019).

Conclusion: The vasoconstrictors initial pressure effect was equivalent and vasopressin maintained a late effect at prolonged resuscitation. Nevertheless, when compared with placebo, only adrenaline significantly increased the ROSC rate. (Arq Bras Cardiol. 2013; 101(6):536-544)

Keywords: Epinephrine; Arginine Vasopressin; Ventricular Fibrillation; Cardiopulmonary Resuscitation; Models, Animal.

Introduction

Epinephrine (adrenaline) was discovered over 100 years ago, and has been used in human cardiopulmonary resuscitation (CPR) since 1922[1]. Vasopressin is also centenary, but its use in resuscitation began in the 1990s[2]. These drugs are vasoconstrictors that enhance vital organs perfusion, increasing the chance for return of spontaneous circulation (ROSC)[3]. It has been observed in animals and humans an association between ROSC rate and coronary perfusion pressure (CPP), which is the pressure gradient between the aorta and right atrium during "diastolic phase" of chest decompression[4,5]. In turn, CPP has a positive correlation with myocardial blood flow measured by radioactive microspheres[6-8].

Adrenaline acts on alpha-2 receptors causing vasoconstriction, and on alpha-1 and beta-adrenergic receptors causing unwanted effects, such as increased oxygen consumption and increased energy depletion of the fibrillating myocardium, among others[9]. Vasopressin causes vasoconstriction when acting on their own V1a receptors located in the vascular smooth muscle, increasing the CPP without the adrenergic undesired effects[9]. Vasopressin vasoconstrictor effect remained equal under prolonged acidosis, in the same conditions in which alpha-adrenergic effect decreased[10]. Knowledge on vasopressin and its cardiac receptors has been growing in the recent decades[11,12].

During the development of a cardiac arrest animal model and resuscitation, we planned this study aiming to evaluate the pressure effect of adrenaline, vasopressin, and the CPR itself or placebo, in addition to observing the cardiac arrest short-term survival. The model was designed in order to simulate an out-of-hospital cardiac arrest in an adult patient with seven minutes downtime until the emergency team arrival. In this pig model of cardiac arrest due to eletrically induced ventricular fibrillation, with exception of the treatment dose regimen, CPR followed the current standards[13].

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Methods

A prospective, randomized, blinded, placebo-controlled study, approved by the ethics committees in the use of animals for research, according to local law and in line with international standards. Thirty-two animals were successfully prepared and subject consecutively to the protocol, one per day and two per week.

Preparation

Large White Landrace pigs were fasted overnight and had free access to water. After intramuscular pre-anesthesia with 5 mg/kg ketamine hydrochloride, and 0.5 mg/kg midazolam, 12.5 mg/kg thiopental was administered in a marginal ear vein. Keeping the animal in supine position, an orotracheal intubation was performed, inserting a N°. 7 cuffed tube. Anesthesia was maintained by continuous intravenous infusion plus 2 mL fentanyl and midazolam boluses, as required, along with pancuronium for muscle paralysis. The animals were mechanically ventilated: positive pressure, 10 mL/kg tidal volume, 40% fraction of inspired oxygen, 3-5 mmHg positive end expiratory pressure, and respiratory rate adjusted to maintain 40-45 mmHg of expired CO_2 ($ETCO_2$).

Following trichotomy, adhesive gel electrodes were placed and electrocardiogram monitoring. The right jugular vein was dissected, and by adaptation of the Seldinger technique, a vascular 8.5 french (F) sheath introducer with hemostatic valve was inserted, through which anesthesia started to be administered. Likewise, the left jugular vein and the right femoral artery received 8.5 F and 6 F sheaths, respectively. Through the left jugular vein, a balloon-tipped 7.5 F Swan-Ganz catheter was advanced to the pulmonary artery. Through the femoral artery and with a guide wire, a 6 F pigtail catheter was advanced to the aortic root. Catheters positioning was guided by the pressure curves. Catheters were connected to pressure transducers, which were previously calibrated with a mercury sphygmomanometer and aligned at bed height.

We used the Swan-Ganz catheter atrial port to monitor right atrial pressure. The pigtail catheter was used to monitor the aortic pressure. A 5 F pacemaker bipolar cable was introduced through the right jugular vein into the right ventricle wall. This position was confirmed when ventricular extra-systoles appear on the monitor. The cable was removed immediately after the electrical induction of ventricular fibrillation, which was obtained by contacting cable poles with a common 9 V battery poles for two seconds.

Data collection

We used an intensive care unit general monitor and an $ETCO_2$ common monitor during the experiment. Electrocardiogram, $ETCO_2$, aortic pressure and right atrial pressure were recorded, along with on-line calculated CPP. These parameters were recorded at 250 samples per second, using a computerized system for biological data collection (MP100 System, Biopac, Inc.).

Pressures and electrocardiogram were collected directly to the system through proper transducers and surface electrodes. $ETCO_2$ was collected through the specific monitor analog output. The system software enabled to perform the measurements later. Heart rate and mechanical ventilation, as well as chest compression rate and manual ventilation with AMBU, were measured over the aortic pressure curve cycles and $ETCO_2$, respectively.

Experimental protocol

The protocol can be seen schematically in Figure 1.

About one hour after preparation, anesthesia was stopped, ventricular fibrillation was induced and the mechanical ventilation was interrupted simultaneously. In order to simulate an out-of-hospital cardiac arrest case with downtime until the emergency team arrival, there was no intervention in the first seven minutes. At 7 minutes, the manual chest compression begun (100 compressions per minute with approximately 5 cm depth), and the
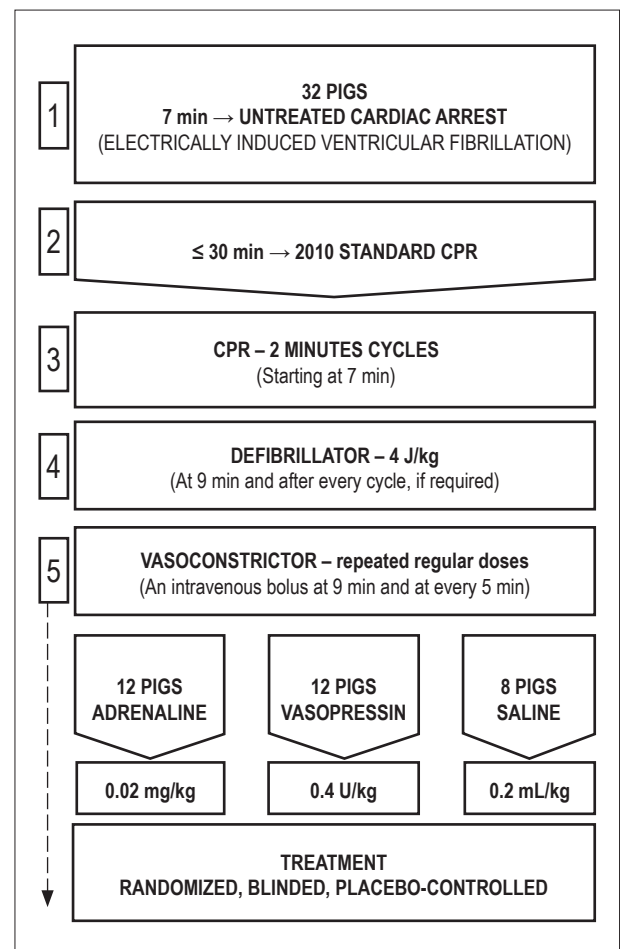

Figure 1 - *Protocol design of experimental cardiac arrest and cardiopulmonary resuscitation (CPR).*

manual ventilation with AMBU (10 ventilations per minute with 100% O_2 at 10L/min flowing into the reservoir). The cardiac massage rate was mantained at about 100 based on listening to appropriate music. After two minutes CPR cycle, a defibrillator (4 J/kg, monophasic) was used once at 9 minutes, immediately followed by another CPR cycle. From the first attempt on, the rhythm was always checked at the end of each cycle, and the defibrillator was used in the same way, if required. Cardiac massage was resumed immediately after each attempt or after each asystole rhythm checking or pulseless electrical activity. At 9 minutes and every five minutes of CPR, an intravenous dose was applied in bolus: 0.02 mg/kg (n = 12 pigs) adrenaline (Epinephrine 1 mg/mL, Cristália); or 0.4 U/kg (n = 12) arginine-vasopressin (Encrise 20 U/mL, Biolab); or 0.2 mL/kg (n = 8) placebo, composed of 0.9% saline solution. The vasoconstrictors dilution in 0.9% saline solution made it possible for each dose to have equal volume of 0.2 mL/kg. Treatment was previously randomized and the protocol participants were blinded regarding which treatment was applied to each animal. The same participant always carried out the cardiac massage in order to avoid interpersonal differences in the massages, although current guidelines recommend switching people in this role. The animals received 5 mg/kg of amiodarone at 11 minutes and 2.5 mg/kg at 16 minutes, if persistent ventricular fibrillation was observed. CPR continued to a maximum of 30 minutes or to the ROSC, which was defined as a suitable heart rhythm and systolic blood pressure higher than 50 mmHg for over 20 minutes. In this case, anesthetic infusion was restarted and mechanical ventilation proceeded according to previous settings, and animals were monitored for 120 minutes. In these two hours, if necessary, 500 mL of 0.9% saline solution was administered rapidly to raise mean arterial pressure above 70 mmHg. No other drug was administered during the entire protocol, with the heparin small doses exception to maintain the catheters patency. At 2 hours following ROSC, the euthanasia was induced by administering 10 mL intravenous bolus of 19.1% potassium chloride.

Systematization of measurements

Measurements were performed after the last experience. The measurement was systematized to occur at 20 seconds before the timepoints marked on the parameters curves, as on the pauses for rhythm checking. To avoid measurement tendencies, the randomization secret was revealed only at the end, after hundreds of measurements performed, and after making the data spreadsheet. Each measurement corresponds to seven seconds or about 10 chest compressions. Measurements were exported with seven digits precision to the statistical program.

Statistical analysis

We used the Number Cruncher Statistical System (NCSS 2007) software package for the statistical analysis. ROSC rate was compared using the chi-square and Fisher's exact test. Adapting a survival curve (Kaplan-Meyer) of 120 minutes with all animals potentially alive during CPR and deaths occurring at 37 minutes, the hazard ratio (HR) of death (Cox-Mantel) was calculated at specific time. The mean ± standard error values of the parameters were compared with repeated measures ANOVA and Bonferroni (with control). Tests were considered significant at $p < 0.05$ (two-tailed). The p-value is presented with three digits and no approximation. The measurements are presented with the appropriate precision and approximation for each parameter.

Results

The animals received similar volumes of anesthetic drugs, about 50 mL of fentanyl and midazolam, and 30 mL of pancuronium, in addition to 2,000 mL of 0.9% saline solution. Baseline pre-cardiac arrest parameters were similar, as can be seen in Table 1.

Table 1 - Pre-cardiac arrest baseline parameters similarity among 32 pigs, according to randomized and blinded treatment applied during cardiopulmonary resuscitation

PARAMETER	ADRENALINE (12 PIGS)	VASOPRESSIN (12)	PLACEBO (8)	p
Weight (kg)	36 ± 0.5	35 ± 0.6	36 ± 0.9	NS
Temperature (°C)	37,6 ± 0.3	38,0 ± 0.4	37,7 ± 0.3	NS
$ETCO_2$ (mmHg)	41 ± 0.5	42 ± 0.6	42 ± 0.7	NS
Respiratory rate (rpm)	24 ± 1.1	23 ± 1.2	21 ± 0.5	NS
Heart rate (bpm)	139 ± 7	127 ± 8	141 ± 9	NS
Aortic pressure (mmHg)	141 ± 4	141 ± 4	134 ± 9	NS
R-Atrial pressure (mmHg)	5 ± 0,4	5 ± 0.6	5 ± 0.7	NS

$ETCO_2$: expired carbon dioxide; NS: not significant; mean ± standard error.

ROSC rate

ROSC was observed in 18 animals that survived without cardiac events up to 120 minutes, such as spontaneous ventricular fibrillation, for example. The ROSC rate differed (p = 0.031) among groups: adrenaline (10/12), vasopressin (6/12), and placebo (2/8). ROSC rate increased following adrenaline compared with placebo (p = 0.019), and it did not differ following vasopressin compared with placebo or adrenaline, as can be seen in Figure 2.

Coronary perfusion pressure

After CPR starting, pressure increased equally in all groups up to 9 minutes when vasoconstrictors were administered, and the pressure level raised even more, as can be seen in Figure 3.

The first dose of vasoconstrictors significantly increased CPP compared with placebo, and with no significant difference between adrenaline and vasopressin. Pressure level remained above 30 mmHg up to 13 minutes, or until four minutes since first dose. After 19 minutes, successive vasoconstrictors doses did not increase CPP. The vasopressin effect remained close to 20 mmHg, but adrenaline effect ended at the third dose, when the pressure level dropped to near zero. The CPR plus placebo effect reached approximately 20 mmHg and lasted only few minutes.

Time, doses and return of circulation

The time (and standard error) from cardiac arrest to ROSC was similar among the three groups: adrenaline, 15 minutes and 45 seconds (50 seconds); vasopressin, 18 minutes and 12 seconds (152 seconds); placebo 14 minutes and 18 seconds (72 seconds). The 18 animals mean was 16 minutes and 24 seconds (59 seconds), and median was 15 minutes and 28 seconds; minimum of 13 minutes and 6 seconds, maximum of 29 minutes and 4 seconds. Only one animal had time-to-ROSC extended to over 19 minutes.

Most animals received one or two doses of treatment untill achieving ROSC, and with no difference among count of doses per group: adrenaline, 1.6 (0.2); vasopressin, 1.8 (0.5); and placebo, 1.5 (0.5). Fourteen animals received six doses and had no ROSC.
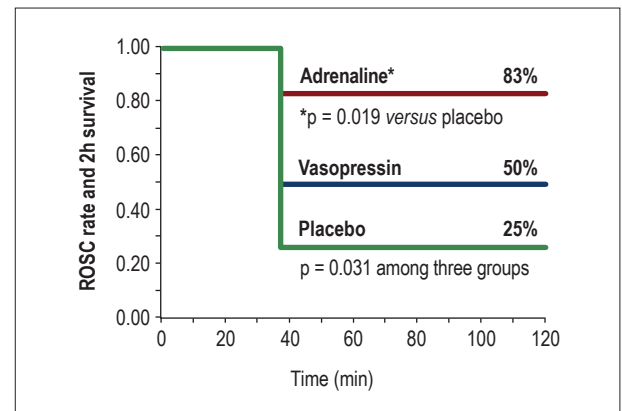

Figure 2 - *Return of spontaneous circulation (ROSC) rate and survival curve adaptation of pigs in ventricular fibrillation, potentially alive during resuscitation efforts and with all deaths occurring at 37 minutes, according to randomized and blinded treatment.*
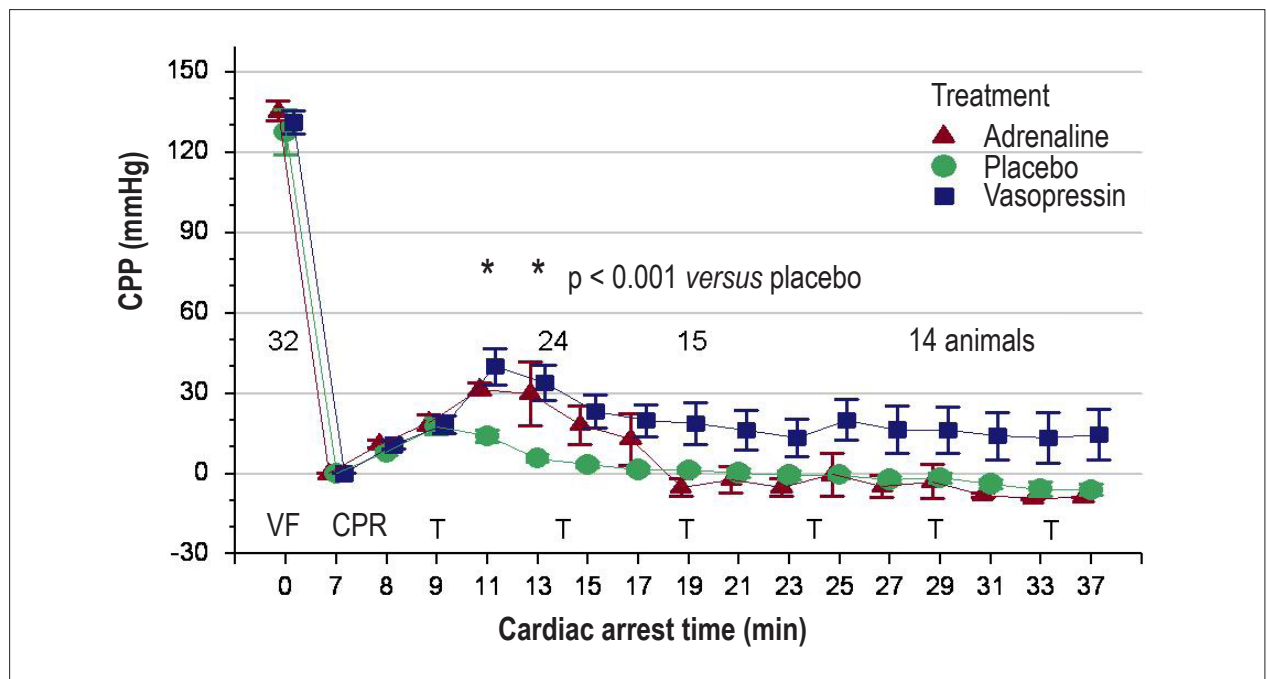

Figure 3 - *Coronary perfusion pressure (CPP) mean ± standard error, pre-cardiac arrest at time zero, and during cardiopulmonary resuscitation (CPR) initiated at 7 minutes of ventricular fibrillation (VF), according to randomized and blinded treatment applied (T) repeatedly. Asterisks indicate timepoints of pressure increase with vasoconstrictors, wich remained significant with vasopressin. The pigs count decreases until 14 animals that not resuscitated: adrenaline 2/12, vasopressin 6/12, and placebo 6/8.*

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The ROSC occurred up to eight minutes of CPR in 2/3 cases, corresponding to four cycles of cardiac massage, or up to three defibrillation attempts. The animals that achieved ROSC received successive shocks and no previous rhythm was observed other than ventricular fibrillation. The cumulative ROSC rate can be observed in Figure 4.

Other parameters monitored during CPR

As it can be seen in Figure 5, other parameters did not differ among treatment groups, except for the aortic pressure, which defined the CPP, since atrial pressure remained close to 20 mmHg for all time.

The mean cardiac massage rate (and standard error) was 99.5 (0.1) compressions per minute, and manual ventilation rate was 10.5 (0.1) ventilations per minute. As these rates, $ETCO_2$ did not differ among groups, increasing during the first massage cycle and then progressively decreasing.

Cardiac arrest nonsurvival hazard ratio

Compared with placebo, the cardiac arrest nonsurvival risk decreased with adrenaline (HR = 0.22, 95% CI 0.05 - 0.91, p = 0.043), and it did not differ with vasopressin (HR = 0.67,

95% CI 0.21 - 2.12). Adrenaline significantly reduced the risk by 78%, and vasopressin reduced by 33%, but with no statistical significance. Between these vasoconstrictors there was no difference about short-term survival.

Post-cardiac arrest parameters

Up to two hours after achieving ROSC, the animals showed no statistical significant difference in physiological parameters among treatment groups, as can be seen in Table 2.

Discussion

The results of this study were interesting about CPR itself consistent pressure effect, and about initial equivalence of both vasoconstrictors. It was observed that CPR raised pressure level to the threshold that favors ROSC chance, and two placebo-treated animals survived for two hours. Vasoconstrictors increased pressure level even more, and the risk of cardiac arrest nonsurvival decreased with both treatments, significantly with adrenaline. It was observed also that adrenaline has lost its pressure effect after the third dose; vasopressin maintained a significant pressure effect during 30 minutes of CPR; and placebo, *i.e.*, CPR
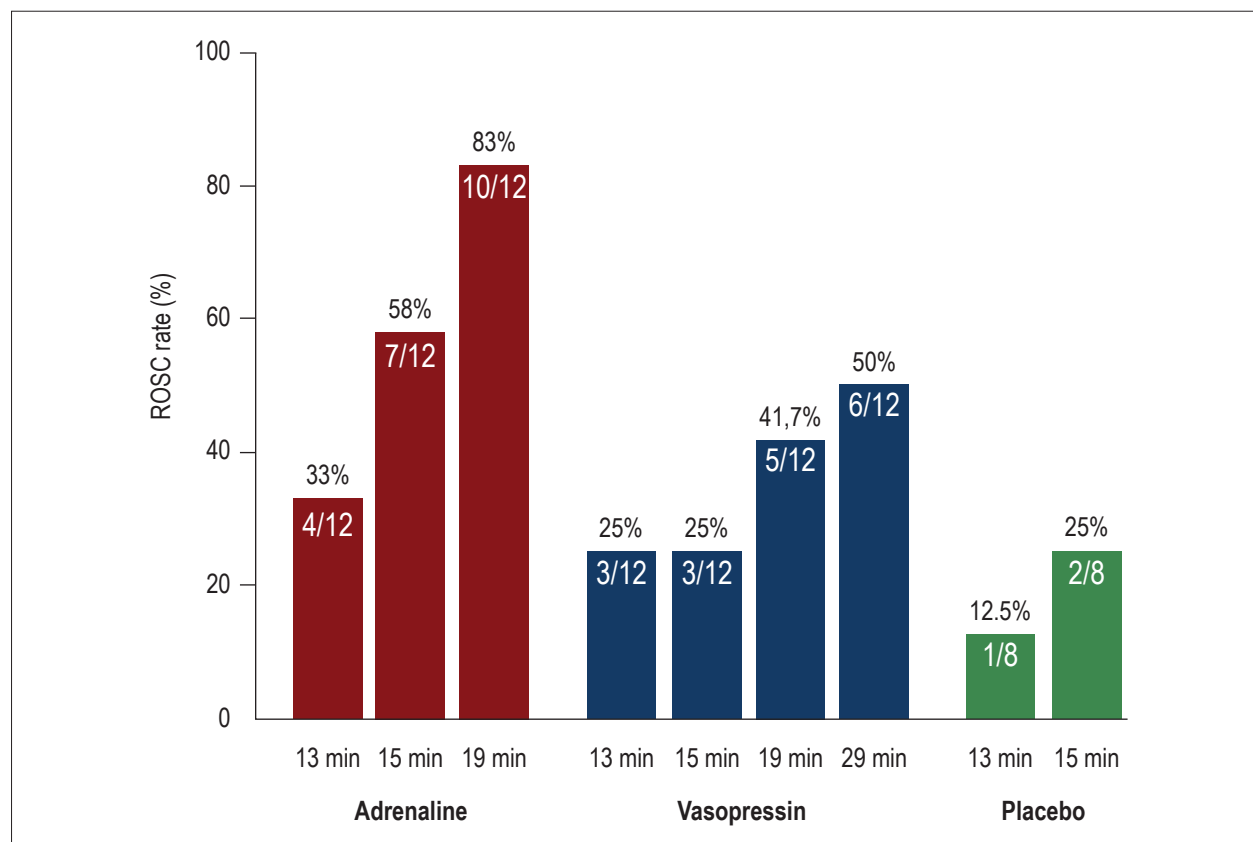

Figure 4 - *Return of spontaneous circulation (ROSC) rate accumulated until the last resuscitated pig in each treatment group.*
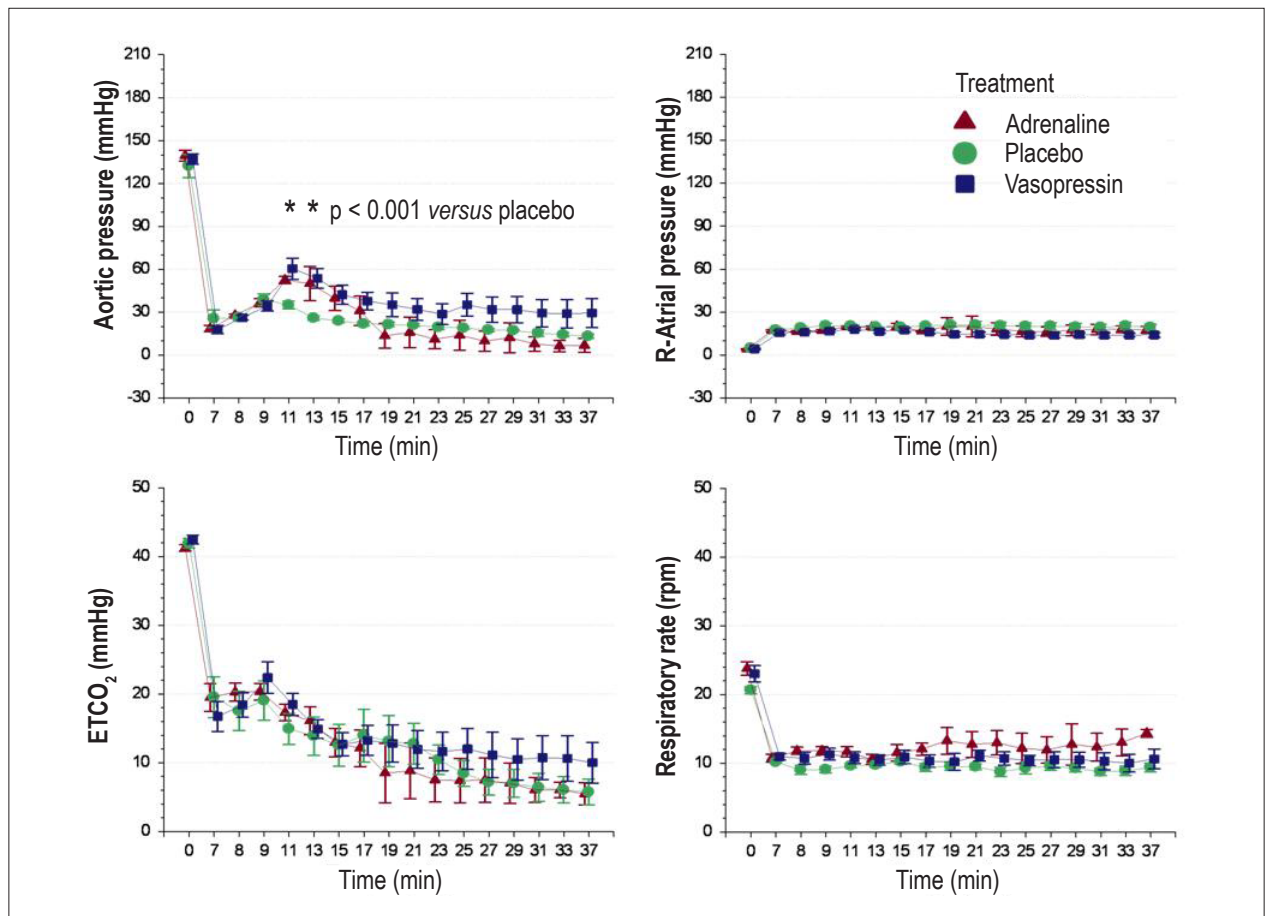
Figure 5 - *Parameters: mean ± stardard error of pressures, expired carbon dioxide (ETCO₂), and respiratory rate, pre-cardiac arrest at time zero, and during cardiopulmonary resuscitation started at 7 minutes, according to randomized and blinded treatment applied in pigs electrically induced to ventricular fibrillation. Manual chest compression rate was similar (99.5 ± 0.1). Following vasoconstrictors treatment at 9 minutes, there was significant effect (compared with placebo) on the aortic pressure only.*

itself maintained a pressure effect during few minutes. In other studies, pressure effects similar to these have been observed[14-18]. It is important to highlight that blood concentration of endogenous epinephrine and vasopressin increases during CPR[19,20].

In the current study, even with initial equivalent vasoconstrictors pressure effect, and even with all similar parameters, only adrenaline significantly increased ROSC rate, and so, it deserves some considerations.

About this resuscitation study model

Swine species was chosen due to it human similarities, like anatomical, physiological, cardiovascular, and mechanical of the chest wall during massage, in spite of the natural species antidiuretic hormone be lysine instead of arginine-vasopressin[21,22]. During the conception of this local study model of resuscitation, it seemed appropriate to evaluate each vasoconstrictor separately because there were several vasopressin half-life related uncertainties, mainly during CPR. Reference literature quotes half-lifes as from four to 24.1 minutes[23, 24]. During CPR, lack of in human knowledge on repeated-doses-vasopressin pharmacokinetics led to stablished one-dose only use[25].

Dose regimen

It was observed equivalent pressure effect between the two initial doses of epinephrine and vasopressin (Figures 3 and 5), but only vasopressin kept effect of about 20 mmHg up to the end of CPR. Repeated doses, considering the prolonged vasopressin half-life, did not cause a cumulative effect of CPP increasing, but maintained stable pressure level for 30 minutes. However, with the same adrenaline dose regimen, CPP level dropped to placebo similar level, despite repeated doses. In other CPR studies, it was also observed a brief adrenaline effect and a sustained vasopressin effect[15,26,27].

Cardiac arrest time is critical

The ROSC rate can be influenced by several factors, especially by the circulatory arrest time *(no flow)* and CPR time *(low flow)*[28,29]. In this study, attention was given to every protocol timepoint, so that there would not be any groups difference, but is not possible to control time-to-ROSC. To check whether there was influence of treatment on time-to-ROSC, this time was precisely measured, and no groups difference was observed. Therefore, the adrenaline ROSC rate advantage was not due to differences in duration of ischemia.

Table 2 - Pre (baseline) and post-cardiac arrest parameters similarity among 18 pigs treated with adrenaline (10 animals), vasopressin (6), or placebo (2)

PARAMETER	POST-CARDIAC ARREST TIME						
Treatment	Baseline	10 min	20 min	30 min	60 min	90 min	120 min
Temperature (°C)							
Adrenaline	37.5 ± 0.4	37.9 ± 0.4	38.1 ± 0.4	38.3 ± 0.4	38.6 ± 0.4	38.8 ± 0,4	38.9 ± 0.4
Vasopressin	38.7 ± 0.3	39.1 ± 0.3	39.2 ± 0.3	39.4 ± 0.3	39.6 ± 0.2	39.8 ± 0,2	39.9 ± 0.3
Placebo	38.4 ± 0.5	38.1 ± 1.2	38.5 ± 0.9	38.9 ± 1.0	39.1 ± 1.2	39.3 ± 1,1	39.4 ± 1.2
ETCO$_2$ (mmHg)							
Adrenaline	42 ± 1	41 ± 1	42 ± 1	42 ± 1	43 ± 1	43 ± 1	43 ± 1
Vasopressin	43 ± 1	35 ± 3	37 ± 3	41 ± 2	44 ± 1	45 ± 1	42 ± 1
Placebo	41 ± 2	39 ± 1	41 ± 4	37 ± 5	44 ± 2	41 ± 3	40 ± 1
Respiratory rate (rpm)							
Adrenaline	24 ± 1	23 ± 1	23 ± 1	23 ± 1	23 ± 1	24 ± 1	24 ± 1
Vasopressin	25 ± 2	25 ± 2	25 ± 2	25 ± 2	24 ± 2	24 ± 2	26 ± 2
Placebo	21 ± 1	21 ± 1	21 ± 1	21 ± 1	19 ± 3	21 ± 3	21 ± 3
Heart rate (bpm)							
Adrenaline	138 ± 8	127 ± 10	135 ± 6	130 ± 5	134 ± 8	135 ± 6	143 ± 6
Vasopressin	141 ± 10	129 ± 15	130 ± 13	139 ± 12	151 ± 8	170 ± 13	159 ± 11
Placebo	145 ± 31	128 ± 6	140 ± 18	133 ± 30	128 ± 25	118 ± 35	130 ± 35
Aortic pressure (mmHg)							
Adrenaline	139 ± 5	99 ± 8	101 ± 8	99 ± 7	97 ± 6	106 ± 6	112 ± 6
Vasopressin	140 ± 8	82 ± 11	83 ± 8	95 ± 5	100 ± 6	99 ± 6	97 ± 7
Placebo	163 ± 15	117 ± 2	111 ± 1	116 ± 9	122 ± 15	126 ± 14	132 ± 25
R-Atrial pressure (mmHg)							
Adrenaline	4 ± 1	9 ± 1	9 ± 1	8 ± 1	7 ± 1	6 ± 1	6 ± 1
Vasopressin	4 ± 1	10 ± 1	9 ± 1	9 ± 1	8 ± 1	7 ± 1	7 ± 1
Placebo	3 ± 1	9 ± 1	9 ± 1	7 ± 1	6 ± 1	5 ± 1	4 ± 1

ETCO$_2$: expired carbon dioxide; mean ± standard error.

Perfusion pressure and return of circulation

The duration of ischemia was similar, but the intensity may have been different. In the microcirculation, local differences in specific receptor density and stimulation intensity may explain the difference in the ROSC rate, since similar values of perfusion pressure can coexist with different myocardial blood flows, depending on the vasoconstrictor and on the dose[6,8,11,12]. Despite initial equivalent pressure effect and overall parameters similarity, it was observed an improve in short-term survival with adrenaline *versus* placebo, and it did not differ with vasopressin *versus* placebo. Between vasopressin and adrenaline, there was no significant difference in ROSC rate and short-term survival.

This animal model and two clinical studies

Recently, Jacobs et al. compared adrenaline (n = 272 patients) with placebo (n = 262) in a randomized and double-blind clinical trial[30]. Survival to hospital discharge did not differ, but ROSC chance (23.5% *versus* 8.4%) was higher with adrenaline *(odds ratio* = 3.4, 95% CI 2.0 - 5.6). ROSC rates were smaller than it were in this laboratory study. This can be due to initial rhythms and downtime until CPR, which were unfavorable in clinical setting. These are important differences, so that the vasoconstrictor observed result in clinical setting (23.5% of ROSC) did not even exceed the placebo result in this laboratory study (25% of ROSC). In both studies, it was observed that adrenaline significantly improved ROSC rate.

In another randomized study, adrenaline (n = 158) was compared with vasopressin (n = 178) in four doses of 0.045 mg/kg and 0.8 U/kg at every 5-10 minutes, respectively[31]. The study did not compare vasoconstrictor with placebo. As occurred in the laboratory, vasoconstrictors ROSC rates did not differ (26.6% *versus* 28.7%).

Final considerations

This experimental study model has some limitations: animals are previously healthy, but in clinical setting, there are usually other associated diseases; and duration of ischemia is usually longer; this study was not designed to measure vital organs perfusion or monitor cerebral perfusion pressure, much less the late survival or neurologic function; a group with alternate or combined adrenaline and vasopressin was not defined. Even so, the current study suggests that vasoconstrictors can be more effectively used, and that further studies are required to better understand this question.

Conclusion

In a pig model of cardiac arrest and 2010 standard cardiopulmonary resuscitation, repeated doses of adrenaline or vasopressin were equivalent for initial blood pressure increase. Adrenaline lost its effect at the third dose, unlike vasopressin that maintain its pressure effect following each one of six doses. Without vasoconstrictors, manual chest compression generated pressure for a few minutes. In spite of that, compared with placebo treatment, the ROSC rate and cardiac arrest short-term survival were improved with adrenaline, and it did not differ with vasopressin.

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Author contributions

Conception and design of the research, analysis and interpretation of the data: Palácio MAG, Paiva EF, Timerman A; acquisition of data: Palácio MAG, Paiva EF, Azevedo LCP; statistical analysis and writing of the manuscript: Palácio MAG; obtaining funding: Palácio MAG, Timerman A; critical revision of the manuscript for intellectual content: Palácio MAG, Paiva EF, Azevedo LCP, Timerman A.

Potential conflict of interest

No potential conflict of interest was reported.

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Study association

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