EXPERIMENTAL WORK

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$PetCO_2$, VCO_2 and CorPP Values in the Successful Prediction of the Return of Spontaneous Circulation: An Experimental Study on Unassisted Induced Cardiopulmonary Arrest

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Abstract

Introduction: During cardiac arrest, end-tidal CO_2 ($PetCO_2$), VCO_2 and coronary perfusion pressure fall abruptly and tend to return to normal levels after an effective return of spontaneous circulation. Therefore, the monitoring of $PetCO_2$ and VCO_2 by capnography is a useful tool during clinical management of cardiac arrest patients.

Objective: To assess if $PetCO_2$, VCO_2 and coronary perfusion pressure are useful for the prediction of return of spontaneous circulation in an animal model of cardiac arrest/cardiopulmonary resuscitation treated with vasopressor agents.

Methods: 42 swine were mechanically ventilated (FiO_2=0.21). Ventricular fibrillation was induced and, after 10 min, unassisted cardiac arrest was initiated, followed by compressions. After 2 min of basic cardiopulmonary resuscitation, each group received: Adrenaline, Saline-Placebo, Terlipressin or Terlipressin + Adrenaline. Two minutes later (4th min of cardiopulmonary resuscitation), the animals were defibrillated and the ones that survived were observed for an additional 30 min period. The variables of interest were recorded at the baseline period, 10 min of ventricular fibrillation, 2nd min of cardiopulmonary resuscitation, 4th min of cardiopulmonary resuscitation, and 30 min after return of spontaneous circulation.

Results: $PetCO_2$ and VCO_2 values, both recorded at 2 min and 4 min of cardiopulmonary resuscitation, have no correlation with the return of spontaneous circulation rates in any group. On the other hand, higher values of coronary perfusion pressure at the 4th min of cardiopulmonary resuscitation have been associated with increased return of spontaneous circulation rates in the adrenaline and adrenaline + terlipressin groups.

Conclusion: Although higher values of coronary perfusion pressure at the 4th min of cardiopulmonary resuscitation have been associated with increased return of spontaneous circulation rates in the animals that received adrenaline or adrenaline + terlipressin, $PetCO_2$ and VCO_2 have not been shown to be useful for predicting return of spontaneous circulation rates in this porcine model.

Keywords: Heart Arrest, Induced. Cardiopulmonary Resuscitation. Capnography. Epinephrine.

Abbreviations, acronyms & symbols	
ADR	=Adrenaline
AHA	=American Heart Association
CA	=Cardiac arrest
CorPP	=Coronary perfusion pressure
CPR	=Cardiopulmonary resuscitation
DC	=Decreased cardiac output
IMV	=Invasive mechanical ventilation
$PetCO^2$	=End-tidal CO_2
ROSC	=Return of spontaneous circulation
TP	=Terlipressin
VF	=Ventricular fibrillation
V/Q	=Ventilation/perfusion ratio

INTRODUCTION

Cardiac arrests occur daily in large numbers in several countries of the world and, for the most part, result in death. Cardiopulmonary resuscitation (CPR) is proposed by the American Heart Association (AHA) as an easy intervention, with the goal of reducing the number of deaths, despite discouraging statistics showing that only a small number of patients survive after this event. The use of methods that assess the effectiveness of CPR and that are preferably non-invasive, indicating the metabolic state and the dynamics of the cardiovascular system, would be of great value. Essentially, CPR consists of manual compressions of the patient's thorax, in an effort to help create an artificial anterograde blood flow, combined with either a non-invasive ventilation technique (*e.g.*, mouth-to-mouth) or invasive

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mechanical ventilation in order to oxygenate the blood that reaches the lungs[1].

Capnography presents itself as a non-invasive method, applicable at the bedside, that allows for the assessment of cardiorespiratory status both in experimental[2-6] and clinical studies[7-12]. In addition, it is considered an indicator and/or guide for decisions that enables the assessment of the quality of the CPR maneuvers[13]. Capnography evaluates and monitors physiological conditions by measuring exhaled CO_2 through an infrared light sensor. CO_2 excretion (VCO_2) and partial pressure of CO_2 at the end of the exhalation ($PetCO_2$) are indicative of O_2 consumption by the oxidative metabolism in the tissues and those values are closely related to the pulmonary ventilation/perfusion ratio (V/Q); hence, it is expected that both will increase in an effective CPR. Therefore, the monitoring of exhaled CO_2 has been proposed and used as a non-invasive method to assess cardiorespiratory function, especially in situations of decreased cardiac output (DC), such as during shock and CPR, and its use is compulsory in Surgical Centers[14].

Capnography has been regarded as a potentially useful monitoring method in evaluating the effectiveness of CPR maneuvers, despite limitations and controversies surrounding the subject[15]. Animal and human studies have shown a good correlation between $PetCO_2$ and DC during stages of decreased blood flow and during CPR[16]. $PetCO_2$ can reflect the pulmonary blood flow generated in CPR if CO_2 production and alveolar ventilation are relatively constant during resuscitation maneuvers; however, it is difficult to be measured when CPR is stopped because of changes in the alveolar dead space and minute volume ratio, which affects the correlation between $PetCO_2$ and DC[17].

Some studies suggest that the increase in $PetCO_2$ during CA is a predictor of the success of the CPR. Considering the event of cardiac arrest, CPR and the post-event, we can find several changes in $PetCO_2$ levels. It is known that the values of $PetCO_2$ at the beginning of ventricular fibrillation (VF) fall significantly, and this reduction is attributed to decreased pulmonary blood flow, which is insufficient to carry and eliminate the CO_2 produced in the tissues. Evidently, in extreme cases of low DC, there would also be a lower CO_2 production because of the anaerobic metabolism, given the low O_2 supply to the tissues. Once CPR is started, and it is effective in oxygenating the blood and increasing the tissue flow, $PetCO_2$ values also increase, as an increase in blood flow must occur in the pulmonary capillaries, which in turn results in the exhalation of CO_2. When the return of spontaneous circulation (ROSC) occurs, those values increase significantly, reaching levels comparable to those before CA. These changes are useful to quantify the effectiveness and success of the CPR maneuvers as well as to assess the cardiorespiratory status of the patient after ROSC. It has been observed that there is no survival for a $PetCO_2 < 5$ mmHg[18].

Some studies have mentioned a few factors that can affect the levels of CO_2 eliminated by expiration. Among them, we can mention alveolar ventilation, DC, the area of distribution of blood flow in the body, and the production of CO_2 by tissues. Some authors also reported that the measurement of CO_2 is not able to reflect the certain success of CPR, since the results do not confirm those reported in studies that have measured other parameters[19]. However, capnography is still used and regarded as the best and most effective non-invasive method of measuring the elimination of CO_2 in Emergency Rooms, Surgery Centers, and ICU in cases of CA, being considered essential when performing CPR, for decision-making, assessment of its initial success (ROSC), and subsequent clinical evolution (cardiorespiratory stabilization).

The objective of this study was to assess if $PetCO_2$, VCO_2, and coronary perfusion pressure (CorPP) values are useful in predicting the success of ROSC in an animal model of CA/CPR using vasopressor agents.

METHODS

This study was approved by the Institutional Review Committee for Experiments with Animals (EAEC-IB-Unicamp-1276-1/2007) and it was conducted in the laboratory of Experimental Surgery and Medicine, School of Medical Sciences – Universidade Estadual de Campinas (UNICAMP), São Paulo, Brazil.

The methods used were the same as the ones described in the novel article of Ovalle et al.[20], using forty-two Large-White, immature swine, weighing approximately 20 kg, which presented ROSC. Under anesthesia with ketamine (10 $mg.kg^{-1}$ intramuscularly) and thiopental (25 $mg.kg^{-1}$ intravenously), the animals were intubated endotracheally and ventilated with FiO_2=0.21 (and positive pressure at the end of exhalation of 0 cmH_2O), a fixed respiratory rate (10 cpm), and a tidal volume ranging from 15 to 20 mL/kg (Ventilator DX-3010®, Dixtal, Brazil), in order to maintain a $PetCO_2$ between 36-44 mmHg (Respiratory Profile Monitor CO_2SMO Plus 8100®, Dixtal/Novametrix, Respironics, Murrisville, PA, USA). Surgical vascular catheterizations were performed to measure pressure in the thoracic aorta and the right atrium (DX-2020®, Dixtal, Brazil).

Using a bipolar pacemaker placed on the right ventricular cavity, we induced VF, which remained without assistance for 10 minutes. Then, the animals were kept in the supine position and reattached to the mechanical ventilator, and we started CPR (100 compressions/10 ventilations/min, continuously, without alternating with chest compressions).

After two minutes, the animals were allocated into four groups (randomized and blind), receiving via central IV: Group 1 - Adrenaline (ADR – 45 $\mu g.kg^{-1}$); Group 2 - saline-placebo (10 ml); Group 3 - Terlipressin (TP* – *Glypressin®, Laboratórios Ferring Ltda., Brazil – 20 $\mu g.kg^{-1}$); and Group 4 - TP (20 $\mu g.kg^{-1}$) + ADR (45 $\mu g.kg^{-1}$). All drugs were diluted in saline solution (10 ml), in equal syringes, thus the main resuscitator did not know what drug was being administered.

Two minutes after injecting the drugs, defibrillation was performed with sequential shocks (every 15 seconds) of 200 J (Biphasic Defibrillator, Cardiomax, Instramed, Brazil), until ROSC, a pace other than VF was obtained or 2 minutes of attempts had elapsed. We set the return of spontaneous circulation as the recovery of spontaneous heart rate with a systolic blood pressure ≥ 60 mmHg for ≥ 5 minutes. The animals were considered as survivors when they remained alive, with a systolic blood pressure ≥ 60 mmHg, without the use of additional vasopressor agents for 30 minutes after ROSC.

During spontaneous circulation, CorPP was calculated as the difference between mean arterial pressure and mean central venous pressure. During CPR maneuvers, CorPP was calculated as diastolic arterial pressure (decompression) minus central venous pressure (decompression)[21]. At the completion of the experiment, all animals resurrected were killed with an overdose of thiopental and 19.1% potassium chloride.

Statistical Analysis

Initially, we performed a descriptive analysis, presented in the form of tables with frequency and measures of the location and dispersion of values. For comparison of the parameters assessed in only one moment between the groups, we used the Kruskal-Wallis test. For comparison of the parameters measured among the groups and times, we used the analysis of variance (ANOVA) for repeated measures, with transformation by posts, followed by multiple comparisons through the Tukey test for the location of differences between groups and the profile test for contrasts for the location of the differences between times. To verify the difference between proportions, we used Fisher's exact test. Statistical tests were bilateral and the significance level adopted was 5% (P<0.05).

RESULTS

In Table 1, we describe the values of the following variables:

- $PetCO_2$ (mmHg) measured at baseline (before induction of CA), two minutes of CPR (before the injection of drugs), and 4 min of CPR (2 min after the injection of drugs and immediately before ventricular defibrillation); there were no statistically significant differences between the groups;
- VCO_2 (mL/min) measured at baseline (before induction of CA), two minutes of CPR (before the injection of drugs), and 4 min of CPR (2 min after the injection of drugs and immediately before ventricular defibrillation); although there was a statistically significant decrease in VCO_2 at 2 min and 4 min of CPR in relation to baseline, there were no statistically significant differences between the groups at any moment;
- CorPP (mmHg) measured at baseline (before induction of CA), two minutes of CPR (before the injection of drugs), and 4 min of CPR (2 min after the injection of drugs and immediately before ventricular defibrillation). A statistically significant increase in CorPP between the 2 min of CPR (before the injection of drugs) and 4 min of CPR (2 min after the injection of drugs) was observed in the ADR and ADR+TP groups compared to the placebo and isolated TP groups (which was equal to placebo);
- Baseline rectal temperature (°C): ADR: 39.0±0.7; Placebo: 39±0.5; TP: 39.3±0.6; and ADR+TP: 39.6±0.4 (P=0.2085).

Those same variables are shown in Figures 1, 2 and 3.

DISCUSSION

Several studies, both clinical and trial, have investigated the prognostic value of capnography in CA/CPR. The $PetCO_2$ measured by capnography in intubated patients has been

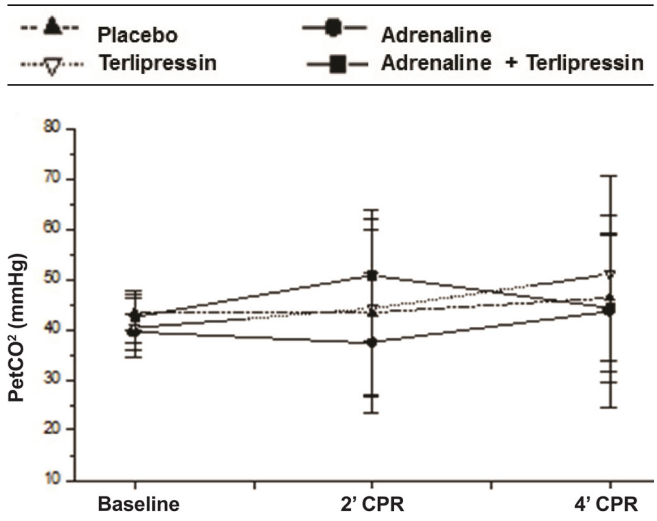

Fig. 1 – *Comparative evolution of the variables assessed at baseline (0), 2 min of CPR (2) and 4 min of CPR in the groups studied. Average value and standard deviation of $PetCO_2$ in each moment and group.*

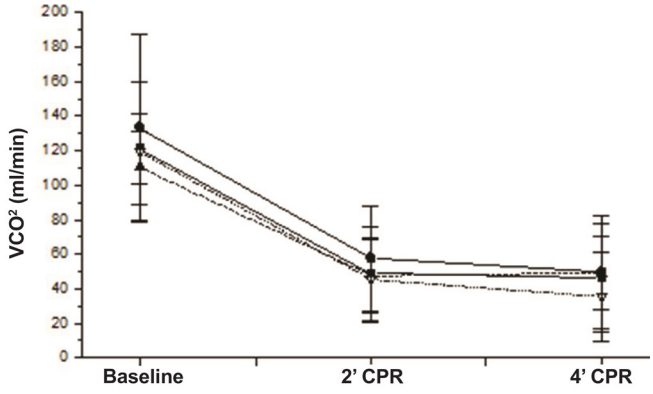

Fig. 2 – *Comparative evolution of the variables assessed at baseline (0), 2 min of CPR (2) and 4 min of CPR in the groups studied. Average value and standard deviation of VCO_2 in each moment and group.*

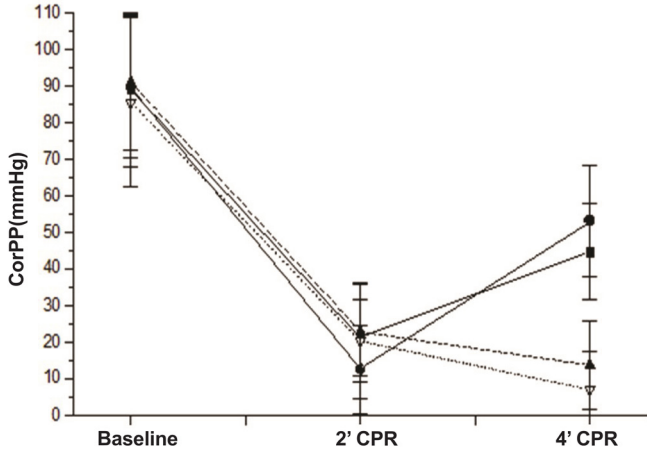

Fig. 3 - *Comparative evolution of the variables assessed at baseline (0), 2 min of CPR (2) and 4 min of CPR in the groups studied. Average value and standard deviation of CorPP in each moment and group.*

Table 1. Descriptive analysis and comparisons of the variables assessed at baseline (0), 2 min of CPR (2), and 4 min of CPR (4) within and among groups.

	ADR + TP (n=11)	ADR (n=10)	Placebo (n=10)	TP (n=11)	*P*
$PetCO_2$ 0*	42.5±5.2	39.4±3.5	43.4±3.5	40.4±6	*
VCO_2 0¥	121.2±20.5	133.4±53.7	110.2±21.2	119.3±40.8	¥
CorPP 0§	88.9±21	89.7±19.5	91.0±18.3	85.5±23.2	§
$PetCO_2$ 2*	50.7±13.1	37.4±14	43.4±16.3	44.2±17.7	*
VCO_2 2¥	48.7±27.5	57.5±30.2	47.5±21.2	45.3±24.5	¥
CorPP 2§	21.3±10.4	12.6±12.1	22.7±13.5	20.2±15.5	§
$PetCO_2$ 4*	44.3±15	43.6±19.3	46.3±12.4	51.0±19.4	*
VCO_2 4¥	46.4±31.1	49.6±32.9	49.2±21.3	35.5±25.5	¥
CorPP 4§	44.6±13.1	53.1±15.2	13.7±12	7.0±10.5	§

ADR=adrenaline; TP=terlipressin; $PetCO_2$=end-tidal carbon dioxide tension (mmHg); VCO_2=carbon dioxide excretion; CorPP=coronary perfusion pressure

* Results of the ANOVA for repeated measurements with transformation for posts:
Effect of group, *P*=0.5427; effect of time, *P*=0.1317; group/time interaction, *P*=0.3043.

¥ Results of the ANOVA for repeated measurements with transformation for posts:
Effect of group, *P*=0.7530; effect of time, *P*=<0.0001; group/time interaction, *P*=0.8622.
Differences between times (profile test for contrast):
Basal ´ 2'CPR, *P*<0.0001; basal ´ 4'CPR, *P*<0.0001; 2'CPR ´ 4'CPR, *P*=0.2286.

§ Results of the ANOVA for repeated measurements with transformation for posts:
Effect of group, *P*=0.0012; effect of time, *P*<0.0001; group/time interaction, *P*<0.0001.
Fixed group and time comparison (profile test for contrast):
Placebo group, *P*<0.0001; Basal ↔ 2'CPR, *P*<0.0001; basal ↔ 4'CPR, *P*<0.0001; 2'CPR ↔ 4'CPR, *P*=0.06.
Adrenaline group, *P*<0.0001; Basal ↔ 2'CPR, *P*<0.0001; Basal ↔ 4'CPR, *P*<0.0014; 2'CPR ↔ 4'CPR, *P*<0.0001.
Terlipressin group, *P*<0.0001; Basal ↔ 2'CPR, *P*<0.0001; Basal ↔ 4'CPR, *P*<0.0001; 2'CPR ↔ 4'CPR, *P*=0.0072.
ADR+TP group, *P*<0.0001; Basal ↔ 2'CPR, *P*<0.0001; Basal ↔ 4'CPR, *P*=0.0003; 2'CPR ↔ 4'CPR, *P*<0.0001.
Setting time and comparing groups (Tukey test):
Basal, without differences, *P*=0.9369; 2'CPR, without differences, *P*=0.2341; 4'CPR, with differences in Placebo and Adrenaline; Adrenaline and Terlipressin; ADR+TP and Placebo; Terlipressin and ADR+TP, *P*<0.0001.

Table 2. Descriptive analysis and comparison of the percentage of survivors among the groups.

Surviving groups	ADR+TP (n=11)	ADR (n=10)	Placebo (n=10)	TP (n=11)	Total (n=42)
No n (%)	2 (18)	2 (20)	8 (80)	10 (91)	22 (52)
Yes n (%)	9 (82)	8 (80)	2 (20)	1 (9)	20 (48)

P<0.0001 (Fisher's test)

correlated with the quality of CPR maneuvers and with ROSC, considering that it is directly related to DC, which in turn is directly related to pulmonary blood flow, $PetCO_2$ being its reflection[22]. However, no experimental model under invasive mechanical ventilation (IMV), with PEEP=0 cmH_2O and FiO_2=0.21, has assessed $PetCO_2$, VCO_2, and CorPP in the prediction of success of ROSC on unassisted CPR for 10 min using terlipressin (a pro-drug, a vasopressin synthetic analogue, with a longer half-life than vasopressin), adrenaline and their combination as vasopressor agents, in addition to placebo.

In several published studies, $PetCO_2$ has proved to be a useful variable in assessing the effectiveness of CPR maneuvers and results in different models of CA.

In the 1980s, Sanders et al.[23] monitored the elimination of CO_2 (VCO_2) in experimental studies of CA/CPR. The elimination of CO_2 was assessed in different types of chest compression,

and the study reported that all types of maneuvers increased $PetCO_2$. Little more than a decade later, Blumenthal et al.[24], also in an experimental study, measured $PetCO_2$ and VCO_2 and concluded that higher values of $PetCO_2$ during and after CPR were associated with a better prognosis.

In our study, there was no statistically significant association between the times and the registered values for $PetCO_2$ with ROSC, although a sudden and immediate increase in $PetCO_2$ at the beginning of the CPR was observed, which expresses the pulmonary blood flow, and thus, DC. The data indicates that $PetCO_2$, both at 2 min and 4 min of CPR (more importantly, because it was after the administration of the drugs), is not correlated with ROSC rates, *i.e*., it was not different among the four groups. Nevertheless, we have to consider that in our study the CA/CPR model was performed on very young (immature) animals, being an extreme CA model, for 10 min without any assistance, and, after this period, the animals were ventilated with an initial FiO_2 (0.21). We should also highlight the fact that we did not alternate between ventilation and compression, which may have compromised the effectiveness of the alveolar ventilation.

In relation to VCO_2 at 2 and 4 min of CPR, it did not differ statistically between the four groups and, therefore, it was not indicative of ROSC. On the other hand, CorPP proved to be significantly higher in the ADR and ADR+TP groups compared to the Placebo and Terlipressin groups at 4 minutes of CPR, which indicates that CorPP was a predictive factor for ROSC.

Human studies use other variables to assess the successful prediction of ROSC. Different criteria are used, but capnography is also the main focus of the prognostic assessment after CA. One of the first studies in the 1980s by Garnett et al.[25] assessed patients under IMV who presented CA, and they concluded that the monitoring of $PetCO_2$ during CPR can be useful and serve as a guide during resuscitation maneuvers.

Another clinical study, conducted by Sanders et al.[26], assessed $PetCO_2$ in patients subjected to CPR. The authors reported that all patients listed and those who presented ROSC showed an average $PetCO_2 \geq 10$ mmHg. None of the patients with an average $PetCO_2 \leq 10$ mmHg presented ROSC. The data in this prospective clinical test indicate that the monitoring of $PetCO_2$ during CPR can be useful in the prediction of ROSC in CPR in humans.

$PetCO_2$ values have been correlated with CorPP and ROSC rate. Thus, in an animal model (dogs) of CA/CPR, Sanders et al.[27], in another study, found a significant correlation ($P<0.01$) between $PetCO_2$ and CorPP. The data in this study were confirmed by the same group, in the same year, with small variations in the method. However, the actual physiological relationship between CorPP and $PetCO_2$ during CPR remains uncertain[23].

In our study, we have observed a significant increase in CorPP ($P<0.0001$) in the 4th minute of CPR (after drugs) in relation to the 2nd min (before drugs) of CPR in the ADR and ADR+TP groups. However, the same behavior was no observed in $PetCO_2$ and VCO_2.

The use of vasopressor agents is suggested in the first cycles of CPR[25]. For different types of CA, vasopressor, adrenaline or vasopressin can be administered in order to increase myocardial and cerebral blood flow. In the study of Ovalle et al.[20], the use of some vasopressor agents during CPR was assessed. It was observed that ADR and its combination with terlipressin, but not isolated terlipressin, were effective in increasing CorPP and ROSC. Furthermore, the ADR+TP combination provided greater hemodynamic stability after ROSC in the surviving animals, suggesting that TP can be a useful drug in handling hypotension after CPR[28].

In most published studies, both clinical and experimental ones, the initial, final, maximum and minimum readings show higher values of $PetCO_2$ in patients who presented ROSC. These authors highlight that clinical studies receive influences from diseases already present in patients, and this factor should be considered[18].

The $PetCO_2$ values assessed in many (clinical and experimental) studies can assist in verifying the effectiveness of CPR maneuvers in order to guide, with due caution, the actual results of resuscitation, since very low $PetCO_2$ values may indicate that there is no more reason to continue the efforts of CPR[29].

In short, $PetCO_2$ and VCO_2 values obtained by volumetric capnography have differed from the findings in some published studies. In addition, those values are not correlated with hemodynamic variables (CorPP) or with ROSC rates in our experimental model with immature swine, in which CA was induced by ventricular fibrillation and the animals remained without assistance for 10 min with subsequent CPR. It should be noted that the animals were under IMV, with FiO_2=0.21 and PEEP=0 cmH_2O, and we used vasopressor agents (ADR and TP; isolated or in association).

CONCLUSION

From the results obtained in the study, both $PetCO_2$ and VCO_2 showed no correlation with ROSC, although VCO_2 was 50% lower during the CPR maneuvers (would it be more sensitive in the detection of a decrease in pulmonary blood flow?). Although we cannot affirm with certainty, some hypotheses were made to explain this fact, namely: FiO_2=0.21 during the entire experiment, immaturity of the animals, time of non-assistance after CA (10 minutes), and positive pressure (IMV) in the CPR, which may have led to an even sharper decrease in the right preload. Thus, further studies are needed to verify the value of volumetric capnography ($PetCO_2$ and VCO_2) to guide the effectiveness of CPR maneuvers, especially with the use of adjuvant vasopressor agents.

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Authors' roles & responsibilities

ACLM Analysis and/or data interpretation; manuscript writing or critical review of its content; final manuscript approval

LCM Analysis and/or data interpretation; manuscript writing or critical review of its content; final manuscript approval

IAP Analysis and/or data interpretation; manuscript writing or critical review of its content; final manuscript approval;

CCISO Conception and design study; realization of operations and/or trials; analysis and/or data interpretation; manuscript writing or critical review of its content

SA Conception and study design; execution of operations and/or trials; analysis and/or data interpretation; manuscript writing or critical review of its content; final manuscript approval;

MMM Execution of operations and/or trials; analysis and/or data interpretation; manuscript writing or critical review of its content; final manuscript approval

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