



Original Contribution

Esmolol does not affect circulation negatively during resuscitation

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ABSTRACT

Background: Experimental studies have combined epinephrine with esmolol to attenuate post-ROSC myocardial dysfunction. Treatment with esmolol during cardiopulmonary resuscitation may be inappropriate due to esmolol's potential depressant effect on circulation. We aimed to compare the effects of epinephrine and esmolol, administered individually, on hemodynamic parameters using a placebo controlled, double blinded, porcine model of cardiac arrest. **Methods:** Thirty pigs were randomized into three groups. After five minutes of untreated cardiac arrest, advanced life support (ALS) compressions and ventilation were initiated. Medication was administered at the beginning of the first, third, fifth, seventh and ninth ALS cycle. The epinephrine group received 20µg/kg epinephrine at every administration, the esmolol group received 0.5mg/kg esmolol at the first administration and isotonic saline subsequently, and the placebo group received isotonic saline. Defibrillation attempts were included from the fourth cycle and onwards. The primary endpoint was end-tidal carbon dioxide (ETCO₂). Secondary endpoints included coronary perfusion pressure (CPP), mean arterial pressure (MAP) and return of spontaneous circulation (ROSC).

Results: The slopes between groups were significantly different over time for both ETCO₂ ($p < 0.001$) and CPP ($p = 0.003$). ETCO₂ deteriorated faster in the epinephrine group compared to esmolol and placebo (p -values < 0.001). CPP was higher with esmolol compared to epinephrine ($p = 0.002$). There was no significant difference in MAP measurements ($p = 0.985$) and the rate of ROSC ($p = 0.151$) between groups.

Conclusions: Esmolol either improved or showed no significant difference regarding all hemodynamic parameters compared to epinephrine and placebo. Our study does not disfavor the use of esmolol as a resuscitative drug.

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1. Introduction

Survival from out-of-hospital cardiac arrest increased from 7.9% to 12.0% between 2010 and 2016 [1,2]. The explanation is likely multifactorial, although uniform guidelines have been shown to improve survival independently [3]. The 2015 International Liaison Committee on Resuscitation guidelines recommend administration of epinephrine during cardiac arrest [4] because of an increased rate of return of spontaneous circulation (ROSC) [5]. The increased rate of ROSC has been linked to the α receptor agonistic effect epinephrine [6]. However, despite the increased rate of ROSC, no effect on survival is seen at hospital discharge [5]. The lack of long-term effect with epinephrine administration is thought to be mediated by post-ROSC myocardial dysfunction [7] secondary to ischemia [8]. Ischemia may result from an increase in myocardial oxygen demand induced by epinephrine's β_1 receptor stimulation [9].

Experimental studies have combined epinephrine with β -blocking agents to reduce the β_1 -agonistic effects of epinephrine and potentially inhibit post ROSC myocardial dysfunction. Recent experimental studies adding the fast acting β -blocking agent, esmolol, to epinephrine, have

shown improvement in both four-hour survival and post ROSC myocardial function in porcine models [10].

Cardiac levels of endogenously produced epinephrine increase to approximately 150 times baseline values during cardiac arrest [11]. Therefore, the adverse effects of epinephrine may be exerted even without exogenously administered epinephrine and treatment with β -blocking agents may prove beneficial even without exogenous epinephrine administration. However, due to esmolol's depressant effect on circulation [12], treatment with esmolol during resuscitation can seem inappropriate. In order to elucidate this effect, we aimed to compare the hemodynamic effects of epinephrine and esmolol during cardiac arrest in a placebo controlled porcine model.

We hypothesized that esmolol would lower the end-tidal partial pressure of CO₂ (ETCO₂) and decrease coronary perfusion pressure as compared with epinephrine in a porcine model of cardiac arrest.

2. Methods

2.1. Study design

The experiment was approved by the National Committee on Animal Research Ethics (2014-15-0201-00421) and carried out in

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accordance with Danish law and guidelines for care and use of animals in experimental studies. The study was a randomized, blinded placebo controlled intervention study. 30 Danish female pigs (median 30.9 kg (interquartile range 30.6–32.0)) were randomized into three groups in a 1:1:1 ratio. These groups were the epinephrine group, the esmolol group and the placebo group. An independent study assistant conducted the randomization prior to study initiation with an online random generator and prepared visibly identical syringes (2 mL) according to randomization. The study investigators were blinded to group allocation throughout the experiment.

2.2. Study preparation

The pigs were fasted overnight but allowed free access to water and sedated with 7.5 mg *s*-ketamine and 15 mg midazolam administered intravenously prior to anesthesia. Anesthesia was induced with pentobarbital (10 mg/kg) and maintained with sevoflurane (end-tidal concentration 2.0–2.2%) and fentanyl (5 µg/kg/h) following endotracheal intubation. During surgical preparation, the pigs were ventilated with a tidal volume of 10 mL/kg, peak end-expiratory pressure of 5 mmH₂O, a fraction of inspired O₂ of 0.35 and a respiratory frequency adjusted to an ETCO₂ of 35–45 mmHg. An isotonic saline infusion (2 mL/kg/h) was administered to compensate insensible perspiration. A body temperature of 38 °C was maintained with an electric heating blanket. Prior to instrumentation a heparin bolus (175 international units/kg) was administered to prevent clotting. Vascular sheaths were inserted in each of the carotid arteries and both jugular veins using the Seldinger technique. A pulmonary artery catheter (Edwards Lifescience, Irvine, CA, USA) was placed via the right jugular vein. The sheath in the right carotid artery was connected to a fluid filled pressure transducer in order to measure arterial pressures. Two solid-state pressure catheters (Ventric-Cath 510, Millar Instruments, USA) were advanced through the left jugular- and carotid sheaths to the right atrium and proximal aorta, respectively. The position of all catheters was verified using X-ray transillumination and pressure curves.

3. Experimental protocol

After surgical preparation, the animals were allowed to equilibrate for 30 min. At the end of the equilibration period, a temporary pacing catheter was placed in the left ventricle via the right carotid sheath and connected to a nine-volt battery until ventricular fibrillation (VF) and cardiac arrest occurred. VF was defined as a rapid decline in mean arterial pressure (MAP) towards zero mmHg and electrocardiographic waveforms corresponding to VF. After successful induction of VF, mechanical ventilation was discontinued, the endotracheal tube was clamped and fentanyl infusion was stopped according to Utstein guidelines [13].

Advanced life support (ALS) cycles were initiated after 5 min of cardiac arrest (Fig. 1). ALS cycles commenced with a rhythm assessment and consisted of 2 min of compressions with a frequency of 100 min⁻¹, ventilation rate of 10 min⁻¹, tidal volume of 10 mL kg⁻¹,

a peak inspiratory pressure of 40 cmH₂O and an inspiratory oxygen fraction of 100%. In addition to this, administration of the intervention medication took place at the beginning of the first, third, fifth, seventh and ninth ALS cycle, corresponding to approximately every fourth minute. Defibrillation attempts were included from the fourth ALS cycle and onwards if a shockable rhythm was observed to imitate a realistic delay to defibrillation. A shock sequence of 200 J, 300 J and 360 J was selected and 360 J was delivered using a biphasic defibrillator during the third and every consecutive shock (Fig. 1).

The epinephrine group received epinephrine (20 µg/kg, 2 mL saline dilution) on every administration. The esmolol group received only a single dose of esmolol (0.5 mg/kg 2 mL saline dilution) at the first administration and 2 mL isotonic saline doses during the following administrations. All piglets were in VF at the first rhythm analysis where esmolol was administered. The placebo group received doses of 2 mL isotonic saline throughout the study.

ROSC was defined as an electrocardiogram showing a spontaneous perfusing rhythm and a MAP >30 mmHg. Animals were categorized as dead if they had not achieved ROSC within ten ALS cycles. Animals with ROSC were observed for 60 min and euthanized with a pentobarbital overdose.

4. Endpoints

The primary endpoint was ETCO₂. Secondary endpoints were the rate of ROSC and all invasive pressures and their derivatives as mentioned below.

ETCO₂ was measured by a mechanical ventilator (S/5 Datex-Ohmeda Avance, GE HealthCare, Horten, Norway). MAP was derived from readings of systolic- and diastolic pressure in the right carotid artery. mPAP and CVP were quantified with the pulmonary artery catheter and end-diastolic proximal aortic pressure and right atrial end-diastolic pressure were measured using the solid state catheters.

ETCO₂, MAP, mean pulmonary artery pressure (mPAP) and central venous pressure (CVP) were stored with S5 Collect software (Datex-Ohmeda, Helsinki, Finland) and calculated as an average of three measurements obtained 30 s after the beginning of each ALS cycle. End-diastolic proximal aortic pressure and right atrial end-diastolic pressure were recorded using a PowerLab station (Millar, Inc., Texas, USA). Coronary perfusion pressure was calculated as the difference between the proximal aortic end-diastolic pressure and the right atrial end-diastolic pressure in accordance with Utstein guidelines [13]. Coronary perfusion pressure was reported as an average of ten consecutive measurements beginning 30 s into every ALS cycle.

4.1. Statistics

Parametric analyses were used throughout as data were normally distributed when assessed with histograms and QQ-plots. A Fischer's exact test was used to evaluate survival between groups. Difference in baseline and peak values between groups were tested with a one-way

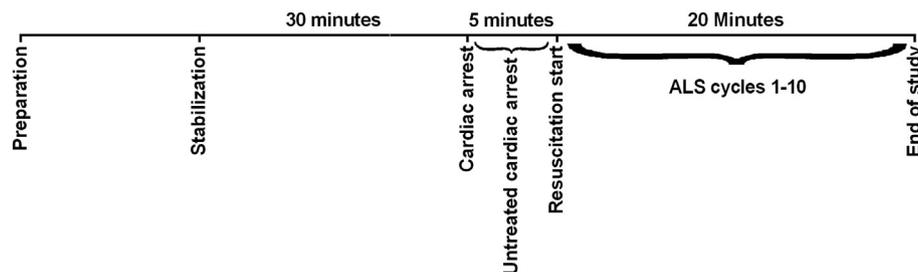


Fig. 1. Flow chart of the experimental protocol. The resuscitation period consisted of a maximum of ten advanced life support (ALS) cycles of 2 min each. The resuscitative cycles consisted of: a rhythm assessment, 2 min of compressions and ventilation. Medication was administered at the beginning of the first, third, fifth, seventh and ninth ALS cycle. Defibrillation attempts were included from the fourth ALS cycle and onwards. Animal achieving return of spontaneous circulation were excluded from further data capture. For further details see the experimental protocol.

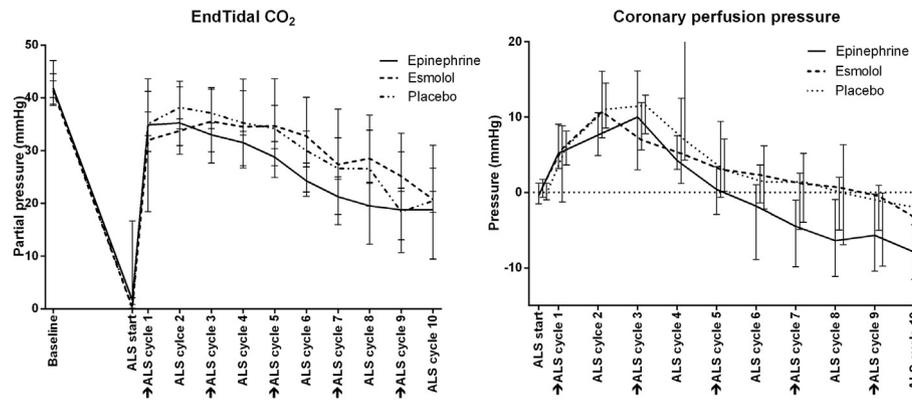


Fig. 2. The effect of epinephrine, esmolol and placebo on end-tidal carbon dioxide (ETCO₂) and coronary perfusion pressure over ten advanced life support (ALS) cycles. ALS cycles were initiated following 5 min of cardiac arrest induced by ventricular fibrillation. p-Values indicate the probability of differences between groups over time (ANOVA for repeated measurements). ETCO₂ ($p < 0.001$) and coronary perfusion pressure ($p = 0.003$). Data is given as median (IQ range). The datapoint *ALS start* represents readings 30 s before resuscitation was initiated. Data was captured 30 s into ALS cycles one to ten. For details on ALS cycles, please refer to experimental protocol. The epinephrine group received epinephrine (20 µg/kg, 2 mL saline dilution) on every administration. The esmolol group received a single dose of esmolol (0.5 mg/kg 2 mL saline dilution) and 2 mL isotonic saline doses in the following administrations. The placebo group received doses of 2 mL isotonic saline throughout the study. Data is given as median (IQ range). Arrows signify administration of study medication.

ANOVA. All repeated measures were analyzed using an ANOVA for repeated measurements. The effects of group, time and the interaction between time and intervention were incorporated. All assumptions for the ANOVA analyses were verified.

All calculations were two-sided and $p < 0.05$ was considered statistically significant. For individual comparisons of the three groups over time, $p < 0.05/3$ defined significance level in accordance with the Bonferroni principle. Statistical analyses were performed using STATA 13 software (StataCorp, LP, College Station USA). Data is presented as median with IQ range.

5. Results

Data was available from all 30 pigs (ten in each group) with few exceptions. Two measurements, one from a pig in the esmolol group (end-diastolic pressure) and one from a pig in the epinephrine group (mPAP) failed due to malfunctioning transducers.

ETCO₂ was similar between groups at baseline ($p = 0.859$), and decreased to zero values following clamping of the tube (Fig. 2). As resuscitation was initiated, ETCO₂ immediately increased to a new maximum and declined throughout successive ALS cycles. The peak values were reached during the first ALS cycle in the epinephrine groups, in the second ALS cycle in the esmolol group and during the third ALS cycle in the placebo group. Peak values did not differ significantly ($p = 0.157$). Overall, the slopes between groups were significantly different over time ($p < 0.001$).

Individual group comparisons yielded a significant difference between the esmolol and epinephrine groups ($p < 0.001$) and between the epinephrine and placebo groups ($p < 0.001$). There was no significant difference between the placebo group and the esmolol group ($p = 0.394$).

Individual comparisons between groups were made for end-tidal partial pressure of CO₂ (ETCO₂), coronary perfusion pressure, mean

arterial pressure, mean pulmonary artery pressure, aortic end-diastolic pressure and right atrial end-diastolic pressure. p-Values are given in Table 1.

A total of seven pigs developed ROSC, none in the epinephrine group, three in the esmolol group and four in the placebo group; $p = 0.151$ for no effect of groups. See Table 2 for details.

Coronary perfusion pressure increased immediately after initiation of chest compressions. In the esmolol group, coronary perfusion pressure peaked during the second ALS cycle and the epinephrine- and placebo groups reached their peak values during the third ALS cycle. Coronary perfusion pressure declined afterwards to a definitive nadir during the tenth ALS cycle in all groups (Fig. 2). There was no significant difference in peak values between groups ($p = 0.168$). The slopes were significantly different over time between groups ($p = 0.003$). When comparing individual groups only the epinephrine- and the esmolol groups were significantly different ($p < 0.001$) (Table 1).

Mean arterial pressure (MAP) was similar at baseline across groups ($p = 0.985$). MAP decreased during cardiac arrest, increased to a new maximum during the first ALS cycle and declined steadily throughout the remaining experiment. In the epinephrine group, the peak was 39 mmHg (33–42), the esmolol group peaked at 36 mmHg (32–41) and the placebo group's maximum was 30 mmHg (26–37) ($p = 0.157$ for no difference). No significant difference was found over time between groups ($p = 0.985$) (Fig. 3).

Mean pulmonary artery pressures were similar at baseline between groups. mPAP increased with cardiac arrest to a new plateau and afterwards declined to a minimum during the tenth ALS cycle (Fig. 3). In the epinephrine group mPAP rose to 37 mmHg (28–62) during the first ALS cycle and decreased to 32 mmHg (24–42) during the tenth ALS cycle. In the esmolol group, mPAP increased to 36 mmHg (28–45) during the first ALS cycle and decreased to 30 mmHg (22–41) in the tenth ALS

Table 1
Individual group comparisons of end-tidal partial pressure of CO₂ (ETCO₂), coronary perfusion pressure, mean arterial pressure, mean pulmonary artery pressure, aortic end-diastolic pressure and right atrial end-diastolic pressure. The epinephrine group received epinephrine (20 µg/kg, 2 mL saline dilution) every fourth minute. The esmolol group received a single dose of esmolol (0.5 mg/kg 2 mL saline dilution) and 2 mL isotonic saline doses every fourth minute thereafter. The placebo group received doses of 2 mL isotonic saline every fourth minute throughout the study.

	Epinephrine group vs. esmolol group	Epinephrine group vs. placebo group	Esmolol group vs placebo group	Overall effect of group
End-tidal partial pressure of CO ₂	$p < 0.001$	$p < 0.001$	$p = 0.394$	$p < 0.001$
Coronary perfusion pressure	$p = 0.002$	$p = 0.057$	$p = 0.100$	$p = 0.003$
Mean arterial pressure	–	–	–	$p = 0.985$
Mean pulmonary artery pressure	–	–	–	$p = 0.503$
Aortic end-diastolic pressure	$p = 0.006$	$p = 0.057$	$p = 0.207$	$p = 0.010$
Right atrial end-diastolic pressure	–	–	–	$p = 0.998$

Table 2

Summary of the occurrence of return of spontaneous circulation within each intervention group according to advanced life support (ALS) cycles. There was no significant difference between groups ($p = 0.151$). For details regarding interventions refer to table 1.

Group	ALS 1–4	ALS 5	ALS 6	ALS 7	ALS 8	ALS 9	ALS 10	Total
Epinephrine	0	0	0	0	0	0	0	0
Esmolol	0	0	1	2	0	0	0	3
Placebo	0	2	0	0	0	1	1	4

cycle. In the placebo group, mPAP increased to 34 mmHg (27–42) during the first ALS cycle and decreased to 23 mmHg (17–29) during the tenth ALS cycle. There was no significant difference between groups ($p = 0.226$) (Table 1).

The effect of epinephrine, esmolol and placebo on mean arterial pressure (MAP), mean pulmonary artery pressure (mPAP), end-diastolic aortic pressure and end-diastolic right atrial pressure over ten advanced life support (ALS) cycles are given in Fig. 3.

6. Discussion

We found that esmolol was equal to or superior to placebo and epinephrine in regard to all hemodynamic parameters as well as the rate of ROSC. During resuscitation, lower ETCO₂ levels as well as lower coronary perfusion pressures were seen in the epinephrine group. These findings were in disagreement with our hypothesis as we had expected treatment with esmolol to reduce both ETCO₂ and coronary perfusion pressure.

ETCO₂ was significantly lower in the epinephrine group during the resuscitation period compared to both esmolol and placebo. This is consistent with other experimental studies where epinephrine reduced ETCO₂ when compared to placebo [14,15]. Lower ETCO₂ during resuscitation has been associated with both low cardiac output [16] and decreases in cerebral perfusion pressure [17]. ETCO₂ is determined by ventilation, metabolic rate and pulmonary blood flow, and if the first two are assumed to have been constant between groups, the changes in ETCO₂ in the epinephrine group were due to a decrease in cardiac output. Epinephrine mediated decrease in cardiac output has been attributed to an increase in pulmonary resistance [14]. This pathophysiological explanation is not substantiated by our results as mPAP was not found to differ across groups ($p = 0.503$). Nevertheless, the previous studies, seen together with the lower ETCO₂ in our study, imply an overall relative weakening of critical hemodynamic parameters during resuscitation with epinephrine.

Coronary perfusion pressure was significantly higher in the esmolol group compared to the epinephrine group. In addition to this, the esmolol group reached its peak coronary perfusion pressure earlier than both other groups. Lower coronary perfusion pressure and low ETCO₂ levels have both been linked with a lower rate of ROSC [18–20]. No pig developed ROSC in the epinephrine group, whereas the corresponding fractions were 4/10 and 3/10 in the placebo- and esmolol groups, respectively.

The beneficial effect of esmolol on coronary perfusion pressure is in line with previous studies that combined beta-blockers and epinephrine. Propranolol given together with epinephrine facilitated either an increase [21–23] or no difference [24] in coronary perfusion pressure

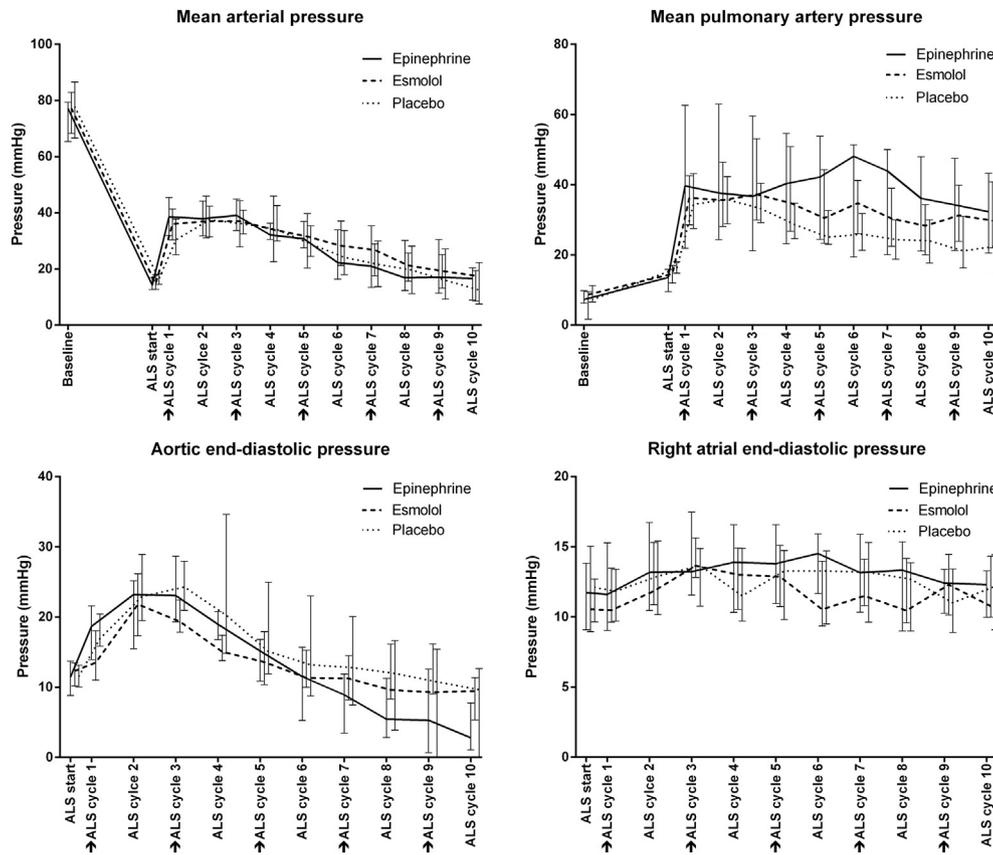


Fig. 3. The effect of epinephrine, esmolol and placebo on mean arterial pressure (MAP), mean pulmonary artery pressure (mPAP), end-diastolic aortic pressure and end-diastolic right atrial pressure over ten advanced life support (ALS) cycles. ALS cycles were initiated following 5 min of cardiac arrest induced by ventricular fibrillation. p-Values indicate the probability of differences between groups over time (ANOVA for repeated measurements) MAP ($p = 0.985$), mPAP ($p = 0.503$), end-diastolic aortic pressure ($p = 0.010$) and right atrial pressure ($p = 0.998$) Data is given as median (IQ range). The datapoint *ALS start* represents readings 30 s before resuscitation was initiated. Data was captured 30 s into ALS cycles one to ten. For details on ALS cycles, please refer to experimental protocol. The epinephrine group received epinephrine (20 µg/kg, 2 mL saline dilution) on every administration. The esmolol group received a single dose of esmolol (0.5 mg/kg 2 mL saline dilution) and 2 mL isotonic saline doses in the following administrations. The placebo group received doses of 2 mL isotonic saline throughout the study. Data is given as median (IQ range). Arrows signify administration of study medication.

when comparing to epinephrine alone. These findings were associated with identical [24] or higher rates of ROSC [23], in groups treated with both beta-blockers and epinephrine.

The lower coronary perfusion pressure in the epinephrine group was caused by a relative decrease in end-diastolic aortic pressure during resuscitation (Fig. 3) and not right-sided pressure differences, confirming previous experimental findings [22]. The low end-diastolic pressure may have been the result of desensitization of adrenergic receptors in the systemic circulation due to an artificially high epinephrine concentration, resulting in a lack of desired vasoconstriction [25]. Early administrations as well as repeated administration of epinephrine have failed to maintain both a high MAP and coronary perfusion pressure in porcine models of cardiac arrest [25–27].

It is noteworthy that aortic end-diastolic pressure differed between groups, whereas MAP did not. MAP was derived from diastolic- and systolic pressures, neither of which exhibited inter-group changes, and was measured in the carotid artery with a fluid filled pressure conductor. Pressure conductors are prone to dampening which may be exacerbated with low flow or pressure, thus introducing a source of random variation and potentially masking a systematic effect. Aortic end-diastolic pressure, in contrast, was quantified using conductance catheters.

To our knowledge no study has compared the effects of esmolol on coronary perfusion pressure and ETCO₂ to epinephrine when given alone during resuscitation. However, several studies have showed similar rates of ROSC when combining administrations of esmolol and epinephrine compared to epinephrine alone [7,10,11,21]. Esmolol improves post ROSC myocardial function assessed by left ventricular contractility [10], and reduces the frequency of post ROSC cardiac arrhythmias in experimental settings [28]. Seen together, experimental data support that esmolol does not influence global hemodynamics adversely during cardiac resuscitation while improving post ROSC results.

7. Limitations of the study

This study was conducted in healthy pigs, which do not represent the human population suffering cardiac arrest. In addition, we used doses of esmolol extrapolated from previous studies combining esmolol with standard doses of epinephrine. The optimal dose of esmolol during resuscitation has not been established. A post-hoc review of the dataset showed that pigs subsequently developing ROSC had the highest levels of both ETCO₂ and coronary perfusion pressure when compared to pigs that did not develop ROSC. In accordance with the experimental protocol, the occurrence of ROSC precluded further invasive data capture. Hence, the results from pigs with the highest levels of ETCO₂ and coronary perfusion pressure were censured to an increasing extent from the seventh ALS cycle and onwards (see Table 2) in both the esmolol- and placebo groups. As no pigs in the epinephrine group developed ROSC, this data censure likely led to more conservative estimate of differences between the epinephrine group and both other groups.

8. Conclusion

End-tidal CO₂ was improved in the esmolol group compared to the epinephrine group and coronary perfusion pressure was significantly higher over time. Other critical hemodynamic parameters were either improved by esmolol or showed no significant difference when comparing to both epinephrine and placebo. Overall this study found that esmolol did not affect circulation negatively during resuscitation and therefore does not disfavor its use as a resuscitative drug.

Declaration of interests

Viktor Kromann Ringgård has no interests to declare. Kristian Borup Wemmelund has no interests to declare. Erik Sloth has no interests to declare. Peter Juhl-Olsen has received minor fees from Novartis and GE for teaching courses not related to the subject in this manuscript.

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