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Experimental paper

The effects of bolus compared to continuous administration of adrenaline on cerebral oxygenation during experimental cardiopulmonary resuscitation

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Abstract

Background: Bolus administration of adrenaline during cardiopulmonary resuscitation (CPR) results in only short-term increases in systemic and cerebral perfusion pressure (CePP) with unclear effects on cerebral oxygenation. The aim of this study was to investigate the effects of bolus compared to continuous adrenaline administration on cerebral oxygenation in a porcine CPR model.

Methods: After five minutes of cardiac arrest, mechanical CPR was performed for 15 min. Adrenaline (45 μg/kg) was administered either as a bolus every five minutes or continuously over the same period via an infusion pump. Main outcome parameter was brain tissue oxygen tension ($P_{bt}O_2$), secondary outcome parameters included mean arterial pressure (MAP), intracranial pressure (ICP), CePP and cerebral regional oxygen saturation (rSO_2) as well as arterial and cerebral venous blood gases.

Results: During CPR, mean MAP (45 ± 8 mmHg vs. 38 ± 8 mmHg; $p = 0.0827$), mean ICP (27 ± 7 mmHg vs. 20 ± 7 mmHg; $p = 0.0653$) and mean CePP (18 ± 8 mmHg vs. 18 ± 8 mmHg; $p = 0.9008$) were similar in the bolus and the continuous adrenaline group. Also, rSO_2 (both 24 ± 6 mmHg; $p = 0.9903$) and cerebral venous oxygen saturation (18 ± 12% versus 27.5 ± 12%; $p = 0.1596$) did not differ. In contrast, relative $P_{bt}O_2$ reached higher values in the continuous group after five minutes of CPR and remained significantly higher than in the bolus group until the end of resuscitation.

Conclusion: Continuous administration of adrenaline improved brain tissue oxygen tension compared with bolus administration during prolonged CPR.

Keywords: Adrenaline, Epinephrine, Advanced cardiac life support, Cardiac arrest, Cardiopulmonary resuscitation, Cerebral perfusion pressure, Intracranial pressure, Brain oxygenation, Near infrared spectroscopy, Oxygen/blood, Pigs

Introduction

Current resuscitation guidelines recommend the administration of 1 mg adrenaline every 3–5 min during adult cardiopulmonary resuscitation (CPR).[1] Through its alpha1-adrenoceptor activity, adrenaline induces vasoconstriction of arterial resistance vessels, thereby increasing systemic perfusion pressures required for organ blood flow. The increase in coronary perfusion pressure, for example, is closely linked to the return of spontaneous circulation and the increase in cerebral perfusion pressure (CePP) is associated with an improvement in cerebral oxygen delivery and cerebral metabolism,[2,3] which are generally considered essential to prevent hypoxic brain damage. However, we along with others demonstrated that the adrenaline-mediated increase in systemic and cerebral perfusion pressures is short-lived and decreases after repeated

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administration,[4–6] which might be one reason of inadequate cerebral blood flow and oxygen delivery during CPR. This is especially true for prolonged CPR, as prolonged periods of no or low flow result in end-organ damage such as hypoxic-ischaemic brain injury, which determines neurological outcomes after successful resuscitation.[7]

Therefore, we aimed to investigate the effects of bolus versus continuous adrenaline administration on cerebral oxygenation during CPR. We hypothesised that continuous administration might improve cerebral oxygenation compared to bolus administration in response to more stable systemic and cerebral hemodynamics. For this purpose, twenty pigs were resuscitated for 15 min, with one group receiving an adrenaline bolus of 45 μg/kg every five minutes and the other group receiving the same dose continuously over the same period using a syringe pump.

Methods

Ethics approval

This pilot animal study was approved by the Institutional Animal Care and Use Committee of the University of Innsbruck and the Austrian Ministry of Science, Research and Economy (Protocol number BMBWF-66.011/0124-V/3b/2018). The study was conducted at the experimental research unit of the Department of Anaesthesia and Intensive Care Medicine of the Medical University of Innsbruck. Experiments were done in compliance with EU regulations for animal experimentation (Directive 2010/63/EU of the European Parliament and the European Council) and reporting is in accordance with current ARRIVE guidelines.

Experiment and animal preparation

This study was conducted on twenty 12- to 16-week-old domestic pigs of both sexes with a median weight of 41.8 kg (IQR 38.8–44.0). The pigs were fasted overnight, but had free access to water. One hour before transport to the study site, they were premedicated with azaperone (4 mg/kg IM; Jansen, Vienna, Austria) and atropine (0.01 mg/kg IM). In the animal laboratory, sedation was intensified with ketamine (30 mg/kg IM) and propofol (0.5–1 mg/kg IV). After insertion of an endotracheal tube (Rüsch, Kernen, Germany) during spontaneous ventilation, general anaesthesia was induced with propofol (3–5 mg/kg IV), fentanyl (10 μg/kg IV) and rocuronium (1 mg/kg IV) and maintained with propofol (5–7 mg/kg/h IV) and remifentanil (0.2–0.3 μg/kg/min IV). Ventilation was volume-controlled (Julian, Draeger, Lübeck, Germany) with 21% inspiratory oxygen, a positive end-expiratory pressure (PEEP) of 5 cm H_2O and a tidal volume of 10 ml/kg body weight. Ventilation rate was adjusted to achieve normocapnia (35–40 mmHg). Normovolaemia was maintained by Elo-Mel isotone (10 ml/kg/h IV; Fresenius Kabi Austria, Graz, Austria). A standard electrocardiogram (ECG) with lead II was used to monitor the heart rhythm and a pulse oximeter was attached to the pig's tail.

Before instrumentation, 1.5 g cefuroxime (Fresenius Kabi Austria GmbH, Graz, Austria) was administered and repeated after four hours to prevent septic complications. After dissection of the scalp and galea aponeurotica, one borehole was made by a neurosurgeon (DP, MB) in the left hemisphere, through which an intracranial pressure probe (Neurovent-P, Raumedic AG, Helmbrechts, Germany) and a brain tissue oxygen catheter (LICOX, Sanova Pharma GmbH, Vienna, Austria) were inserted into the frontal region intraparenchymally. On the skin of the right hemisphere, a near-infrared spectroscopy (NIRS) optode (INVOS™ System, Somanetics Inc., Troy, MI, USA) was attached.

Intravascular instrumentation included a right-jugular central venous catheter (8.5F, Arrow, Reading, PA, USA) and a right-femoral arterial catheter advanced into the lower abdominal aorta (6.0 Fr, Arrow, Reading, PA, USA). An angiography catheter (MP A2, Cordis Cooperation, Miami Lakes, FL, USA) was advanced by a neuroradiologist (BG) under fluoroscopic guidance through a left-femoral venous sheath (6.0 Fr, Arrow, Reading, PA, USA) into the internal jugular vein near the cavernous sinus to obtain cerebral venous blood samples.[8] Intravascular catheters were attached to pressure transducers (Xtrans, Codan, Forstinning, Germany) and calibrated at the level of the right atrium. Haemodynamic and respiratory variables were measured and analyzed using an AS/3 Monitor (Datex-Ohmeda AS/3, GE Healthcare, Buckinghamshire, Great Britain). Blood gases were analyzed with a blood gas analyzer (ABL 800 Flex; Radiometer, Brønshøj, Denmark).

Study protocol

After a stabilization period following instrumentation, baseline values for hemodynamic and cerebral oxygenation parameters were obtained and blood samples taken. Cardiac arrest (CA) was induced by applying a 50 Hz, 60 V alternating current via two subcutaneous needle electrodes. Ventilation and intravenous administration of anaesthetic drugs were stopped at this point. After five minutes of untreated CA, external mechanical chest compression (LUCAS2, Stryker, Redmond, WA, USA) was initiated, delivering a compression depth of 52 mm and a compression rate of 102/min. At the same time, asynchronous mechanical ventilation was started with 100% inspiratory oxygen, a PEEP of 0 cm H_2O, a tidal volume of 10 ml/kg body weight and a rate of 10/min. The bolus group received three boluses of 45 μg/kg adrenaline at minutes 1, 6 and 11 of CPR, while the continuous group received the same dose (45 μg/kg/5 min intravenously) continuously via a syringe pump. CPR was performed for 15 min before the animals were euthanised with potassium chloride.

Measurement parameters

Main outcome parameter was the partial pressure of oxygen in brain tissue ($P_{bt}O_2$). Secondary outcome parameters included mean arterial pressure (MAP), intracranial pressure (ICP), CePP and NIRS-derived regional oxygen saturation (rSO_2), as well as arterial and cerebral venous blood samples. All monitor parameters were measured continuously and analyzed every five seconds, whereas blood gases were obtained at baseline, after five minutes of CA, and every five minutes during CPR. CePP was calculated as the difference between MAP and ICP. $P_{bt}O_2$ values are presented as relative values to baseline to account for inter-individual differences.

Statistical analysis

Statistical analyses were conducted using R, version 4.0.3 (The R Foundation, Vienna, Austria). All statistical assessments were two-sided and a significance level of 5% was used. Baseline characteristics are presented as medians with 25th and 75th percentiles. The Wilcoxon rank sum test was applied to assess differences between groups and estimated median differences with 95% CIs (confidence intervals) are reported as effect sizes. To assess the differences between groups according to the multiple measurements over time, linear mixed-effects models with the group as fixed effect and random intercepts for measurement time points as well as *subjects* were fitted, with the difference in group effects presented as effect size.

Additionally, the *subject*-induced standard deviation of the estimated group effects is reported alongside the *p* value.

Results

Sixteen of 20 pigs were included in the final analysis (bolus group $n = 8$ and continuous group $n = 8$). Four animals had to be excluded. One animal in the bolus group suffered cardiac tamponade during instrumentation and one animal in the continuous group had fever over 40°. In one animal from each group, the LUCAS2 device released during CPR due to a technical problem resulting in relevant delays in resuscitation efforts. All baseline variables were comparable between the two study groups (Figs. 1 and 2). Baseline BGA values are listed in Table 1.

Mean arterial pressure

MAP dropped with induction of CA and slowly increased with CPR in both groups (Fig. 1). In the bolus group, there was a marked increase within 60 s after the first administration of adrenaline. The increase in MAP subsided just as quickly and was much less pronounced after the second and the third bolus. Interestingly, peak values between animals differed by up to three times. In the continuous group, MAP increased more slowly reaching a plateau three minutes after the start of administration. During the first five minutes of CPR, mean MAP was 49 ± 9 (*subject*-induced standard deviation)

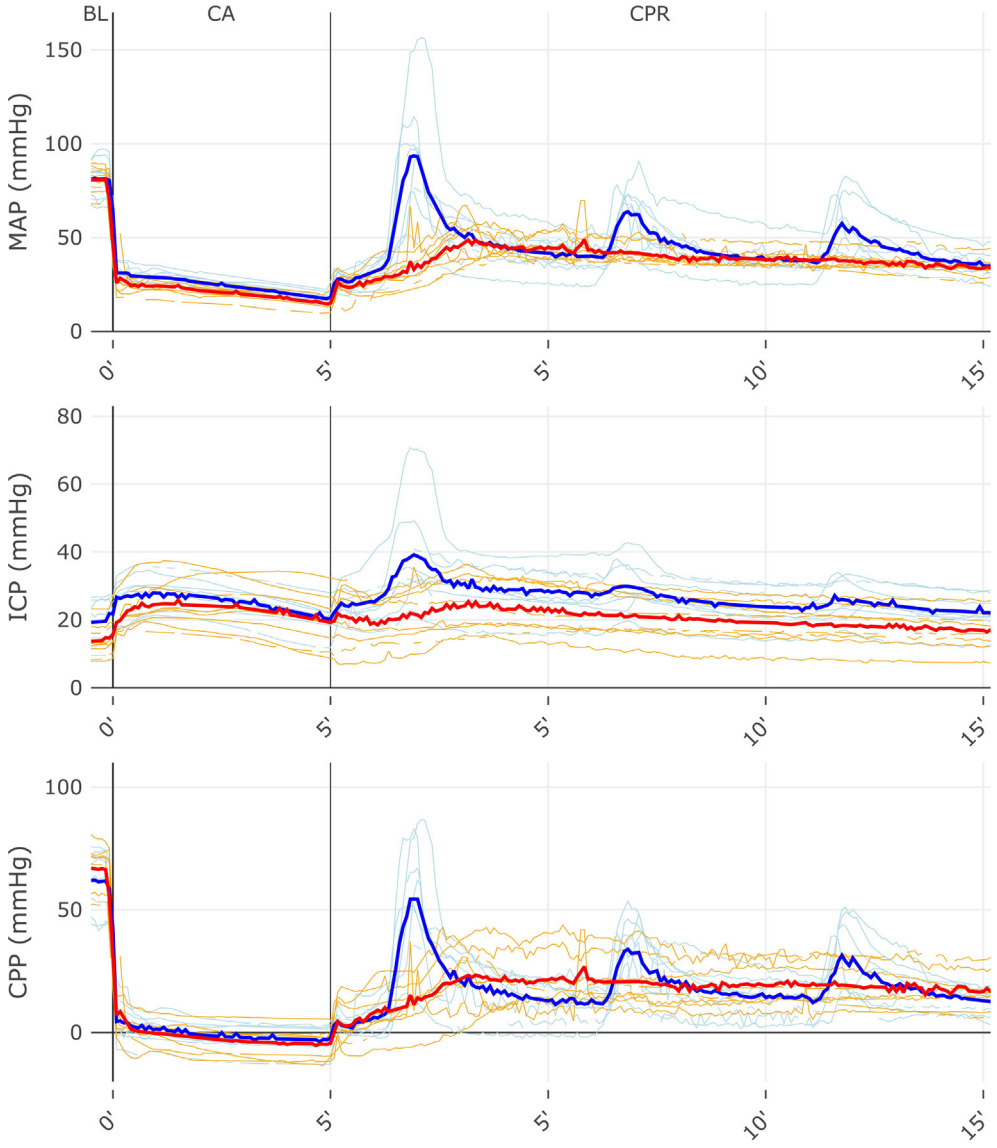

Fig. 1 – Shown are the mean courses of mean arterial pressure (MAP), intracranial pressure (ICP) and cerebral perfusion pressure (CePP) of the animals in the bolus (blue) and continuous adrenaline group (red), as well as the corresponding individual curves. BL denotes baseline, CA cardiac arrest and CPR cardiopulmonary resuscitation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

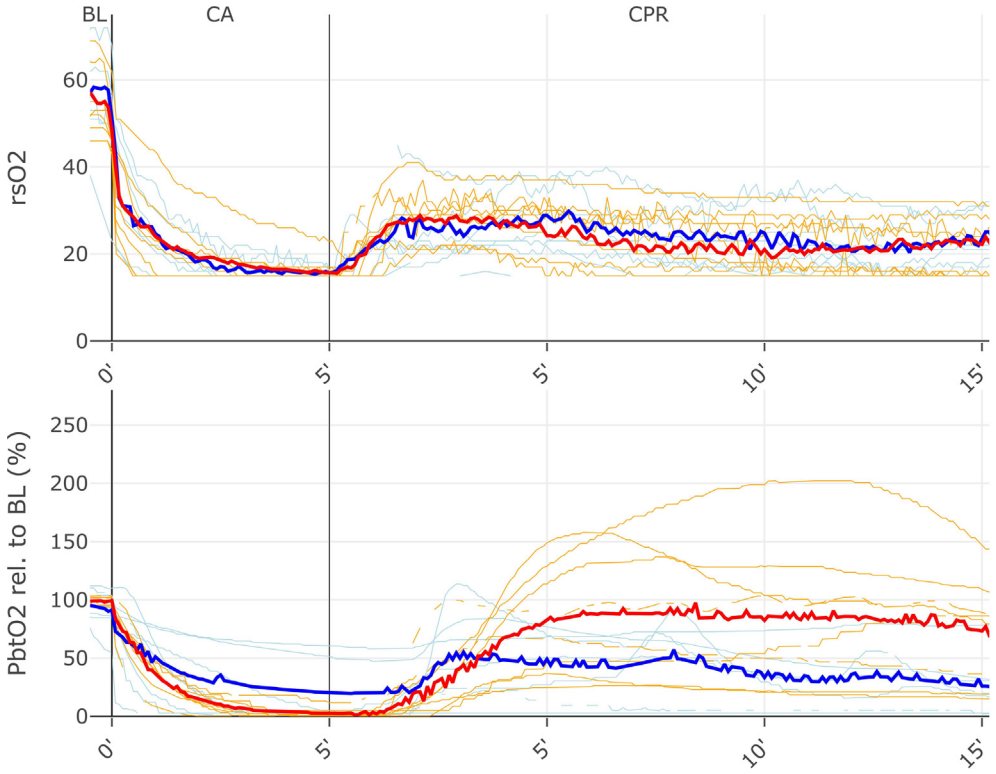

Fig. 2 – Shown are the mean courses of cerebral regional oxygen saturation (rSO_2) and relative partial pressure of oxygen in brain tissue ($P_{bt}O_2$) of the animals in the bolus (blue) and continuous adrenaline group (red), as well as the corresponding individual curves. BL denotes baseline, CA cardiac arrest and CPR cardiopulmonary resuscitation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1 – Baseline blood gas parameters of the bolus and continuous adrenaline group. Data are presented as medians (25–75th percentile) and estimated differences with 95% confidence intervals (CI) assessed by Wilcoxon Rank Sum Test. Hb_a denotes haemoglobin in arterial blood; p_aO_2 and $p_{cv}O_2$ as well as p_aCO_2 and $p_{cv}CO_2$ partial pressure of oxygen and carbon dioxide in arterial and cerebral venous blood; S_aO_2 and $S_{cv}O_2$ arterial and cerebral venous oxygen saturation; Lac_a and Lac_{cv} lactate in arterial and in cerebral venous blood.

Variables	Bolus (n = 8)	Continuous (n = 8)	Estimate with 95% CI	p value
pH	7.52 (7.51–7.53)	7.51 (7.5–7.52)	0.01 (−0.01 to 0.03)	0.2006
Hb_a (g/dl)	8.8 (8.4–9.3)	8.9 (7.9–9.3)	0.1 (−0.9 to 1.4)	0.7278
p_aO_2 (mmHg)	97 (88–106)	94 (91–102)	−1 (−12 to 17)	0.8621
p_aCO_2 (mmHg)	37 (36–39)	36 (34–38)	1 (−2 to 4)	0.4175
S_aO_2 (%)	97.4 (97.1–97.7)	97.1 (96.9–98.1)	0.0 (−1.2 to 1.2)	0.8607
Lac_a (mmol/l)	1.4 (1.2–1.6)	1.4 (1.3–2)	−0.2 (−1 to 0.3)	0.4495
$p_{cv}O_2$ (mmHg)	44 (41–47)	49 (47–53)	−5 (−12 to 4)	0.1206
$p_{cv}CO_2$ (mmHg)	43 (39–45)	41 (39–43)	1 (−3 to 6)	0.6852
$S_{cv}O_2$ (%)	63.1 (60.2–74.1)	78.4 (65.2–80.3)	−6.4 (−19.9 to 4.9)	0.152
Lac_{cv} (mmol/l)	1.6 (1.3–1.8)	1.6 (1.4–2.1)	0 (−1 to 0.3)	0.4478

and 36 ± 9 mmHg (p = 0.0223), during the following five minutes 45 ± 7 and 41 ± 7 mmHg (p = 0.2791) and during the last five minutes 42 ± 7 and 37 ± 7 mmHg (p = 0.1865) in the bolus and in the continuous group, respectively.

Intracranial pressure

ICP was comparable in both groups after five minutes of CA (p = 0.4396). With administration of adrenaline it increased to apparently higher levels in the bolus group, while it remained stable in the

continuous group (Fig. 1). During the first five minutes of CPR, mean ICP was 30 ± 8 and 22 ± 8 mmHg (p = 0.0661), during the following five minutes 27 ± 7 and 21 ± 7 mmHg (p = 0.0924) and during the last five minutes 24 ± 6 and 18 ± 6 mmHg (p = 0.071) in the bolus and in the continuous group, respectively.

Cerebral perfusion pressure

CePP dropped to zero with CA and slightly increased with initiation of CPR (Fig. 1). In the bolus group, it rapidly increased after adrenaline administration, but decreased just as quickly to pre-adrenaline values. Again, this increase was less pronounced after the second and the third bolus of adrenaline. In the continuous group, CePP increased more slowly and reached a steady plateau after three minutes. During the first five minutes of CPR, mean CePP was 19 ± 9 and 15 ± 9 mmHg (p = 0.3736), during the following five minutes 18 ± 9 and 20 ± 9 mmHg (p = 0.679) and during the last five minutes 18 ± 8 and 19 ± 8 mmHg (p = 0.8574) in the bolus and in the continuous group, respectively.

Cerebral regional oxygen saturation

Cerebral rSO_2 decreased during CA and increased in both groups during the first minute of CPR (Fig. 2). Administration of adrenaline had no effect on rSO_2, which remained at the same level in both groups throughout the resuscitation period (both 24 ± 6; p = 0.9903).

Partial pressure of oxygen in brain tissue

Baseline $P_{bt}O_2$ was 9.9 ± 6.5 mmHg in bolus group and 11.4 ± 6.5 mmHg mmHg in the continuous group (p = 0.6351). Relative $P_{bt}O_2$ decreased in all animals during CA (Fig. 2). In the bolus group, relative $P_{bt}O_2$ started to increase approximately one minute after the first adrenaline bolus and reached its highest value of 50% of baseline one minute thereafter. The second and third adrenaline bolus had only a small effect on relative $P_{bt}O_2$, which gradually decreased to below 30% of baseline by the end of the experiment. In the continuous group, relative $P_{bt}O_2$ increased more slowly, but reached 80% of baseline four minutes after the start of administration and remained at this level until the end of the protocol. During the first five minutes of CPR, mean relative $P_{bt}O_2$ was 33 ± 22% and 34 ± 22% (p = 0.9376), during the following five minutes 43 ± 45% and 87 ± 45% (p = 0.0802) and during the last five minutes 31 ± 45% and 83 ± 45% (p = 0.0461) in the bolus and in the continuous group, respectively.

Cerebral venous oxygen saturation

$S_{cv}O_2$ decreased during CA and further during CPR in both groups. Mean $S_{cv}O_2$ over the entire resuscitation period was 18 ± 12% in the bolus group and 27.5 ± 12% in the continuous group (p = 0.1596). Blood gas values are shown in Table 2.

Discussion

This experimental CPR study investigated the pharmacodynamic effects of bolus versus continuous administration of an equal dose of adrenaline on systemic and cerebral hemodynamics and cerebral oxygenation. The most important finding was that continuous administration resulted in higher brain oxygen tension than bolus administration when resuscitation time exceeded ten minutes. Bolus dosing resulted in a rapid and pronounced but short-lived peak in perfusion pressures, which decreased with repeated administration. Of note, the peak values of perfusion pressures differed significantly between bolus animals. Continuous administration on the other hand produced relatively constant increase in blood pressure.

Our findings indicate that the mode of administration of the same dose of adrenaline may be a determining factor for cerebral oxygen delivery during CPR. One possible explanation why continuous administration resulted in better brain oxygenation could be that CePP values were more stable and did not fluctuate as with bolus administration. When CePP fluctuates, periods of high blood pressure may supply the brain with blood and oxygen, but periods of low blood pressure may decrease or even stop CBF, particularly if the pressure falls below the so-called *critical closing pressure* causing brain vessels to collapse.[9] Numerous animal models of CPR have confirmed this idea by showing that adrenaline-induced changes in perfusion pressure are followed by concordant changes in CBF and/or cerebral oxygenation.[4,6,10–14] For example, Gedeborg et al. investigated the effect of adrenaline on cortical CBF using laser Doppler flowmetry and observed transient increases in blood flow

Table 2 – Blood gas parameters of the bolus and the continuous adrenaline group during 15 min of CPR. Values are given as estimated group mean ± subject-induced standard deviation (SD) and estimated differences with 95% confidence intervals (CI) assessed by a linear mixed-effects model. Hb_a denotes haemoglobin in arterial blood; p_aO_2 and $p_{cv}O_2$ as well as p_aCO_2 and $p_{cv}CO_2$ partial pressure of oxygen and carbon dioxide in arterial and cerebral venous blood; S_aO_2 and $S_{cv}O_2$ arterial and cerebral venous oxygen saturation; Lac_a and Lac_{cv} lactate in arterial and in cerebral venous blood.

Variables	Bolus (n = 8)	Continuous (n = 8)	SD	Estimate with 95% CI	p value
pH	*7.17*	*7.16*	*0.07*	*0 (−0.07 to 0.08)*	*0.9489*
Hb_a (g/dl)	12	11.5	*1.1*	*0.5 (−0.5 to 1.6)*	*0.3626*
p_aO_2 (mmHg)	*180*	*227*	*93*	*−47 (−144 to 50)*	*0.3558*
p_aCO_2 (mmHg)	54	51	9	2 (−7.5 to 12)	0.6669
S_aO_2 (%)	90.9	97.0	12.5	−6.1 (−19.6 to 7.4)	0.3954
Lac_a (mmol/l)	9.3	8.9	1.9	0.4 (−1.5 to 2.4)	0.667
$p_{cv}O_2$ (mmHg)	27	35	8	−7 (−16 to 1)	0.1004
$p_{cv}CO_2$ (mmHg)	*82*	*76*	*10*	*6 (−4 to 16)*	*0.2703*
$S_{cv}O_2$ (%)	*18.0*	*27.5*	*12.1*	*−9.5 (−21.9 to 3.0)*	*0.1596*
Lac_{cv} (mmol/l)	*8.1*	*7.7*	*2.1*	*0.4 (−1.8 to 2.6)*	*0.7278*

after each bolus.[4] Notably, cortical CBF returned to pre-adrenaline levels shortly thereafter and blunted with subsequent doses, mirroring the course of perfusion pressures.[4] Exactly the same CBF pattern was described by Mavroudis et al. followed by parallel changes in invasive and non-invasive parameters of cerebral oxygenation.[6] With increasing resuscitation time and decreasing perfusion pressures, CBF and cerebral oxygenation also decreased in their study, confirming the pressure-dependence of blood flow and oxygen supply.

A second and closely related reason could be that the intervals between adrenaline bolus administrations were too long resulting in low perfusion pressure and insufficient blood and oxygen supply to the brain. In fact, CePP dropped to pre-adrenaline levels as early as two minutes after bolus administration and remained there until the next injection. In contrast, continuous adrenaline maintained a relatively constant CePP of approximately 20 mmHg, which was apparently high enough to supply the brain with sufficient blood and oxygen. Already in 1991, Berkowitz et al. studied the effects of continuous adrenaline on cerebrovascular hemodynamics and found that 10 μg/kg/min was necessary to maintain CBF during prolonged CPR.[15] Based on their results, Johansson et al. investigated the effects of bolus versus continuous adrenaline and observed significantly higher mean cortical CBF with continuous administration, but this may simply have been a dosing effect, as significantly different doses of adrenaline were used in this study.[12] In contrast, Nosrati et al. reported improved cerebral oxygenation with bolus adrenaline.[14] However, rather low doses of adrenaline were used in their study and the continuous administration of 3.75 μg/kg/min resulted in significantly lower systemic perfusion pressures than 15 μg/kg once every four minutes. It is known, that low doses of adrenaline preferentially stimulate β-adrenergic receptors, which cause vasodilation, while higher doses activate α-adrenergic receptors and cause vasoconstriction.[16] Taken together, continuous adrenaline appears to positively affect cerebral hemodynamics and cerebral oxygenation during CPR, provided an adequate dose is administered.

Another interesting finding was the very heterogeneous response to adrenaline, which was more pronounced in the bolus group than in the continuous group. While MAP increased dramatically in some animals, it remained rather limited in others, with perfusion pressures differing up to threefold. The phenomenon of a varying reaction to adrenaline has only recently been described. In a retrospective analysis of 200 resuscitations in pigs, O'Brien et al. reported significantly higher diastolic blood pressure values in survivors after the first administration of adrenaline, and suspected the reason to be an increased level of endogenous catecholamines or a stronger vascular reaction.[17] Similarly, Slovis et al. observed a very different blood pressure response following adrenaline bolus dosing, with 30% of the animals not responding at all without any increase in cerebral blood flow.[18] It seems obvious that such highly variable responses in blood pressure and blood flow also affect cerebral oxygenation, which could explain the lower $P_{bt}O_2$ values in our bolus group.

Despite this strong inter-individual differences in adrenaline responsiveness, bolus adrenaline was more effective in increasing MAP during the first five minutes of CPR in our study. This observation may have important implications for the clinical implementation of continuous adrenaline in the treatment of cardiac arrest. As every additional minute of CPR is associated with a lower probability of survival with a good neurological outcome,[19] it seems intuitive to increase perfusion pressures as quickly as possible. An initial bolus of adrenaline in combination with a continuous infusion might combine the advantages of both dosing strategies, on the one hand the rapid increase in perfusion pressures and the associated likelihood of a successful shock,[2] and on the other hand an acceptable oxygen delivery to the brain during prolonged CPR. Future studies may seek to investigate the effect of such an approach on cerebral oxygenation and potentially even neurological outcome.

This study has several limitations. First, cardiac arrest patients usually have a number of cardiovascular risk factors, such as hypertension, diabetes or dyslipidemia,[20] resulting in vascular smooth muscle cell remodelling. The response to vasopressors may therefore be different from the young and healthy pigs used in this study. Second, this experiment was conducted under strictly standardised and optimised conditions that may vary in the clinical setting. However, we consider this to be the strength of this study, as this allowed very accurate and reproducible results to be obtained. Further, brain oxygen probes only measure oxygen tension in a very limited sampling area and do therefore not necessarily allow conclusions about other brain regions. Yet, in the case of generalised hypoxia and/or ischaemia during cardiac arrest, it is reasonable to assume that the values are valid for the whole brain. Finally, the best parameter for monitoring cerebral oxygenation during CPR and for predicting hypoxic-ischemic brain injury after return of spontaneous circulation is not known. Since we did not attempt to achieve a return of spontaneous circulation, we do not know whether higher $P_{bt}O_2$ levels translate into better neurological outcome.

Conclusion

Continuous administration of adrenaline improved brain tissue oxygen tension compared with bolus administration during prolonged CPR. Bolus adrenaline is associated with different inter-individual vasoactive responses.

CRediT authorship contribution statement

Julian Wagner: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Simon Mathis:** Investigation, Writing – original draft, Writing – review & editing. **Patrick Spraider:** Investigation. **Julia Abram:** Investigation. **Stefanie Baldauf:** Investigation. **Daniel Pinggera:** Methodology, Investigation. **Marlies Bauer:** Investigation. **Tobias Hell:** Formal analysis, Data curation. **Pia Tscholl:** Visualization, Formal analysis, Data curation. **Bernhard Glodny:** Methodology, Investigation. **Raimund Helbok:** Writing – review & editing, Methodology. **Peter Mair:** Writing – review & editing, Supervision. **Judith Martini:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Gabriel Putzer:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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