Increased cortical cerebral blood flow by continuous infusion of adrenaline (epinephrine) during experimental cardiopulmonary resuscitation

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Abstract

Objective: To study the effects of continuously administered adrenaline (epinephrine), compared to bolus doses, on the dynamics of cortical cerebral blood flow during experimental cardiopulmonary resuscitation (CPR), and after restoration of spontaneous circulation (ROSC).

Methods: Ventricular fibrillation was induced in 24 anaesthetised pigs. After a 5-min non-intervention interval, closed-chest CPR was started. The animals were randomised into two groups. One group received three boluses of adrenaline (20 μg/kg) at 3-min intervals. The other group received an initial bolus of adrenaline (20 μg/kg) followed by an infusion of adrenaline (10 μg/kg min). After 9 min of CPR, defibrillation was attempted, and if spontaneous circulation was achieved the adrenaline infusion was stopped. Cortical cerebral blood flow was measured continuously using Laser-Doppler flowmetry. Jugular bulb oxygen saturation was measured to reflect global cerebral oxygenation. Repeated measurements of 8-iso-prostaglandin F_2α (8-iso-PGF_2α) in jugular bulb plasma were performed to evaluate cerebral oxidative injury.

Results: During CPR mean cortical cerebral blood flow was significantly higher (P < 0.009) with a continuous adrenaline infusion than with repeated bolus doses. Following ROSC there was no significant difference in cortical cerebral blood flow between the two study groups. No differences in coronary perfusion pressure, rate of ROSC, jugular bulb oxygen saturation or 8-iso-PGF_2α were seen between the study groups.

Conclusions: Continuous infusion of adrenaline (10 μg/kg min) generated a more sustained increase in cortical cerebral blood flow during CPR as compared to intermittent bolus doses (20 μg/kg every third minute). Thus, continuous infusion might be a more appropriate way to administer adrenaline as compared to bolus doses during CPR.

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Keywords: Cardiac arrest; Cardiopulmonary-resuscitation; Cerebral blood flow; Adrenaline; Microcirculation

Resumo

Objetivo: Estudar o efeito da administração contínua de adrenalina, comparada com bólus, na dinâmica do fluxo sanguíneo cortical cerebral durante reanimation cardio-pulmonar experimental (RCP), e após retorno da circulação espontânea (ROSC).

Métodos: Induziu-se fibrilação ventricular em 24 porcos anestesiados. Após um intervalo de 5 min de não intervenção, foi iniciada RCP externa. Os animais foram randomizados em dois grupos. Um grupo recebeu 3 bólus de adrenalina (20 μg/Kg) em intervalos de 3 min. O outro grupo recebeu um bólus inicial de adrenalina (20 μg/Kg) seguido de uma perfusão de adrenalina (10 μg/Kg min). Após 9 min de RCP foi tentada desfibrilação e quando o retorno de circulação foi conseguido a perfusão de adrenalina foi suspensa. O fluxo sanguíneo cortical cerebral foi medido em contínuo por Laser-Doppler. Mediu-se a saturação de oxigênio do bolso jugular de forma a reflectir a oxigenação cerebral global. Fizeram-se medições repetidas da 8-iso-prostaglandina F_2α (8-iso-PG F_2α) no plasma obtido do bolso da jugular para avaliar a lesão oxidativa cerebral. Resultados: Durante RCP o fluxo sanguíneo cortical cerebral foi significativamente maior (P = 0.009) com uma perfusão contínua de adrenalina do que com doses em bólus repetidos. Depois da ROSC não houve diferenças significativas na perfusão sanguínea cortical cerebral entre os dois grupos.

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estudados. Não foram observadas diferenças na pressão de perfusão coronária, taxa de ROSC, saturação de oxigênio do bolbo jugular ou 8-iso-PG F_2α entre os grupos estudados. Conclusiones: A perfusão contínua de adrenalina (10 μg/Kg min) produziu um aumento mais sustentado do fluxo sanguíneo cortical durante CPR em comparação com doses em bólus intermitentes (20 μg/Kg cada três minutos). Portanto, a perfusão contínua pode ser uma via mais apropriada para administrar adrenalina em comparação com doses em bólus durante CPR.

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Palavras chave: Paragem cardíaca; Reanimação cardio-pulmonar; fluxo sanguíneo cerebral; Adrenalina; Microcirculação

Resumen

Objetivo: Estudiar los efectos de la administración contínua de adrenalina (adrenalina), comparándola con dosis en bolos, sobre las dinámicas de flujo sanguíneo cortical cerebral durante reanimación cardiopulmonar experimental (RCP), y después del restablecimiento de la circulación espontánea (ROSC). Métodos: Se indujo fibrilación ventricular en 24 cerdos anestesiados. Luego de un intervalo de 5 minutos sin intervención, se inició RCP a tórax cerrado. Se randomizaron los animales en dos grupos. Un grupo recibió tres bolos de adrenalina (20 μg/kg) intermitente de 3 minutos. El otro grupo recibió un bolo inicial de adrenalina (20 μg/kg) seguido por una infusión de adrenalina (10 μg/kg min). Después de 9 minutos de RCP, se intentó desfibrilación, y si se lograba la circulación espontánea se detenía la infusión de adrenalina. Se midió el flujo sanguíneo cerebral en forma continua usando flujometría laser-doppler. Se midió la saturación de oxígeno en el bulbo jugular para reflejar la oxigenación cerebral global. Se realizaron mediciones repetidas de 8-iso-prostaglandina F_2α(8-iso-PGF_2α) en el plasma del bulbo jugular para evaluar la lesión oxidativa cerebral. Resultados: Durante la RCP el flujo sanguíneo cortical cerebral promedio fue significativamente mayor (P = 0.009) con infusión contínua de adrenalina que con dosis en bolos repetidos. Después de ROSC no hubo diferencia significativa en el flujo sanguíneo cortical cerebral entre los dos grupos de estudio. No se encontró diferencia significativa en presión de perfusión coronaria, tasa de ROSC, saturación de oxígeno en bulbo jugular, o 8-iso-PGF_2α entre los grupos de estudio. Conclusiones: La infusión contínua de adrenalina (10 μg/Kg min ) produjo un aumento más sustancial en el flujo sanguíneo cerebral cortical durante la RCP comparado con dosis en bolos intermitentes (20 μg/kg cada tercer minuto). Así, durante la RCP, la administración continua de adrenalina podría ser la manera más apropiada de administrar adrenalina, comparada con el uso de bolos.

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Palabras clave: Paro cardíaco; Reanimación cardiopulmonar; Flujo sanguíneo cerebral; Adrenalina; microcirculación

1. Introduction

Intermittent administration of adrenaline intravenously (i.v.) is recommended [1] during cardiopulmonary resuscitation (CPR). Adrenaline is mainly given to achieve γ-adrenergic agonist effects. It thereby increases myocardial blood flow [2] and improves chances of achieving restoration of spontaneous circulation (ROSC) [3]. Adrenaline also increases cerebral blood flow [4] and hence oxygen delivery to the brain. It is believed that the increase in cerebral blood flow during CPR may improve neurological outcome after cardiac arrest.

The optimal dose of adrenaline during CPR remains unknown. High doses have been found to increase the rate of ROSC in several experimental studies, but it has failed to improve outcome in clinical studies [5]. Experimental studies have reported increased cerebral blood flow during CPR using high-dose adrenaline [6,7]. In a recent study, however, it was found that regardless if standard or high-dose was given during CPR, cerebral blood flow peaks after 1 min but after approximately 2 min the effect is gone [8]. Current guidelines recommend intermittent injection of adrenaline every 3–5 min i.v. during resuscitation [1]. This dosage interval is obviously inappropriate in relation to the duration of the increase in blood flow generated. A shorter dosage interval would be needed in order to maintain a steady increase in cortical cerebral blood flow, but would be highly impractical. Therefore, continuous infusion appears to be a more appropriate way to administer adrenaline during CPR. Continuous administration has been used in earlier experimental studies [7], but direct comparisons between intermittent and continuous administration have not yet been reported.

Insufficient oxygen delivery to the brain during CPR and following reperfusion after ROSC contributes to poor neurological outcome after cardiac arrest [9]. Oxidative stress is believed to be a major cause of reperfusion injury [10,11]. One of the isoprostanes, 8-iso-prostaglandin F_2α (8-iso-PGF_2α), is increased in several diseases that are supposed to be associated with oxidative injury [12,13]. In a recent study, it was shown that the level of 8-iso-PGF_2α in the jugular bulb can serve as a biomarker of cerebral oxidative injury after cardiac arrest [14].

The aim of this investigation was to study the effects of continuous administration of adrenaline during CPR, compared to bolus administration, on cortical cerebral blood flow and global cerebral oxygen extraction during CPR and after ROSC. We also wanted to compare the degree of cerebral oxidative injury in the two methods of
administration by analysing plasma levels of 8-iso-PGF$_{2\alpha}$ in the jugular bulb. We hypothesised that continuous administration of adrenaline, as compared to bolus administration, would maintain a higher mean level of cerebral blood flow during CPR.

2. Materials and methods

The design of this study and the care and handling of the animals were reviewed and approved by the ethics committee for animal experiments at the University of Uppsala, Sweden.

2.1. Animal preparation

Twenty-four piglets of Swedish country breed of both genders were included in the study. They were 11–15 weeks old and had a mean weight of 24.4±1.6 kg. All animals were fasting with free access to water during the night before the experiment. They were delivered directly to the laboratory by the same supplier on the morning for the experiment. Anaesthesia was induced with an intra-muscular injection of tiletamine and zolazepam 6 mg/kg, xylazine 2 mg/kg, and atropine 0.04 mg/kg. A peripheral ear vein was cannulated for induction and maintenance of anaesthesia, and for fluid administration. Morphine 1 mg/kg and ketamine 100 mg were given i.v. as a bolus injection. Anaesthesia was maintained by continuous i.v. infusion of 8 mg/kg/h of pentobarbital, 0.25 mg/kg/h of pancuronium bromide and 0.5 mg/kg/h of morphine. Water losses were compensated for by a bolus infusion of 30 ml/kg of acetated Ringers solution during 1 h before the experiment and a continuous infusion of 2.5% glucose at a rate of 10 ml/kg/h during the whole experiment. Body temperature was continuously measured with the pulmonary artery catheter and controlled with a heating pad, with the aim of maintaining a core temperature around 38 °C.

The piglets received a tracheostomy and were mechanically ventilated (Servo Ventilator 900C, Siemens-Elema, Solna, Sweden) with a 70/30 mixture of N$_2$O/O$_2$ during preparation. Volume-controlled ventilation was used and the minute ventilation adjusted to maintain the arterial PCO$_2$ within a range of 5.0–5.5 kPa (38–41 mmHg) and a PEEP of 5 cm H$_2$O was applied.

For continuous measurement of cerebral cortical blood flow, a Laser–Doppler flow probe (Periflux® Laser–Doppler flow meter PF2B, Perimed, Stockholm, Sweden) was placed directly over the surface of the right frontal cortex through a burr hole 1 cm anterior to the coronal suture [15]. Laser–Doppler flowmetry is a method for continuous measurement of volume flow [16]. This technique is known to be highly suitable for the study of blood flow dynamics, as described earlier by our research group [17].

A pulmonary artery catheter (CritiCath Ohmeda®, 7 French) was inserted via the right internal jugular vein for pressure monitoring. Catheters were also inserted into the right atrium (7 French) for drug administration and pressure monitoring and into the aortic arch via a branch of the right external carotid artery (18 Gauge) for pressure monitoring and blood sampling. Another catheter (3.8 French) was inserted into the left internal jugular vein and passed retrogradely as far as possible towards the jugular bulb for blood sampling. This technique was used in order to allow continuous blood flow in the vein after insertion of the catheter [18].

All animals in which ROSC was not achieved underwent necropsy in order to detect organ damage or pre-existing illness.

2.2. Measurements

Standard lead II ECG, systemic arterial blood pressure, right atrial pressure and pulmonary artery blood pressure were continuously monitored (Marquette, Solar 8000, Hellige systems, Freiburg, Germany) and recorded (Workbench 3.0, Strawberry Tree Inc., Sunnyvale, CA). The coronary perfusion pressure was calculated as the difference between the diastolic aortic and right atrial pressures measured simultaneously. Cardiac output was measured using the thermodilution technique at baseline and repeatedly during the postresuscitation period. Blood gases (ABL 300, Radiometer, Copenhagen, Denmark) and oxygen saturation (OSM3, Radiometer, Copenhagen, Denmark) were repeatedly collected from the jugular and pulmonary venous blood. Blood samples for analysis of isoprostane concentration were repeatedly collected from the jugular venous blood. The plasma samples were kept frozen at −70 °C until analysis.

2.3. Experimental protocol

Nitrous oxide administration was discontinued after preparation of the animals and the piglets were ventilated with 30% O$_2$ in air. After 45 min, baseline values were obtained. Ventricular fibrillation (VF) was induced with a brief application of an alternating current shock of 40–60 V administered by two subcutaneous needles. Cardiac arrest was defined as VF on the ECG and the loss of arterial pulsation. Ventilation was stopped at the same time. After 5 min of cardiac arrest, external chest compressions were initiated with a frequency of 80/min and ventilation was resumed with 100% O$_2$. The piglets were then randomised into two study groups with 12 piglets in each group. One group received an i.v. bolus injection of 20 µg/kg of adrenaline into the right atrial catheter after 2 min of CPR. At the same time a
continuous infusion of adrenaline at 10 μg/kg min was started via the same route. The infusion was stopped when the piglet achieved ROSC. The other group received three bolus doses of 20 μg/kg of adrenaline i.v. These bolus doses were given 2, 5 and 8 min after the start of CPR. Bolus doses of 0.9% NaCl were given as placebo at 5 and 8 min for the group receiving continuous adrenaline, and a continuous infusion of 0.9% NaCl was provided to the bolus group. The investigator performing chest compressions was blinded regarding assigned treatment. In both groups external defibrillatory shocks of 200 J were administered after 9 min of CPR. If two unsuccessful defibrillatory attempts were made, the energy for defibrillatory shocks was raised to 360 J. If ROSC was not accomplished after 11 min of CPR another bolus injection of adrenaline was given via the same route. Defibrillatory shocks were applied over a maximum period of 5 min. CPR was discontinued if ROSC was not achieved during this time (Fig. 1). ROSC was defined as a pulsatile rhythm with a systolic aortic blood pressure greater than 60 mmHg maintained for at least 10 min. In animals that achieved ROSC, FIO2 was reset to 0.3 after 5 min of ROSC. If the arterial pH was less than 7.20, 5 min after ROSC, acidosis was corrected with a tris buffer mixture (Tribonate®, Pharmacia & Upjohn, Stockholm, Sweden) of 1 mmol/kg and by increasing minute ventilation, aiming at an arterial PCO₂ of 5.0–5.5 kPa (38–41 mmHg). No other interventions were done during the observation period.

2.4. Radioimmunoassay of 8-iso-PGF₂α

The isoprostanes are a family of prostaglandin derivatives synthesised through non-enzymatic free radical catalysed oxidation of arachidonic acid [19]. Unextracted plasma samples were analysed for 8-iso-PGF₂α by a highly specific and validated radioimmunoassay at our laboratory as described elsewhere [20]. The detection limit of the assay was about 23 pmol/l.

2.5. Analysis and statistics

Fisher’s exact test was used for comparison of the rate of ROSC between groups. Student’s t-test was used for comparison of different doses of adrenaline between the groups. Cortical cerebral blood flow was recorded every fifth second during resuscitation and the area under the curve was calculated for CPR before intervention (a 2-min period), for CPR during intervention (a 7-min period), and for the postresuscitation phase (a 4-h period). From each area under the curve, a mean level was determined. The Shapiro–Wilk test for normality was used on all variables before further statistical analysis, and if this test was significant, the normal probability plot was assessed. When applicable, a residual plot was also assessed to ascertain the normal distribution of residuals. Results are presented as means (± standard deviation) for variables that are approximately normally distributed, and otherwise as medians (range). Covariance analysis (Proc GLM, SAS Institute Inc., Cary, NC) was used to analyse differences between groups. The baseline level for each variable before the interventions was tested as the covariate in the statistical model and used when appropriate (P < 0.15). The jugular vein oxygen saturation and coronary perfusion pressure were analysed using repeated measurements analysis (Proc Mixed, SAS Institute Inc.).

3. Results

There was no difference in the rate of ROSC between the bolus group (9/12) and the group that received a continuous infusion of adrenaline (7/12) (P = 0.67). All pigs that achieved ROSC survived the entire 4-h
observation period. One pig in the bolus group that achieved ROSC received a fourth bolus dose of adrenaline. The total amount of adrenaline given during CPR was 1.44±0.05 mg in the bolus group and 2.19±0.09 mg in the continuous group (P < 0.001). Systemic acidosis was corrected in eight animals in the bolus group and six animals in the continuous group (NS).

3.1. Cortical cerebral blood flow

During CPR, adrenaline administered as a continuous infusion resulted in a sustained increase in cortical cerebral blood flow that lasted throughout the entire resuscitation period (Fig. 2). Mean cortical cerebral blood flow during CPR was significantly higher (P = 0.009) in the group receiving a continuous infusion as compared to the group receiving repeated bolus doses (Figs. 2 and 3). Repeated bolus doses of adrenaline generated a peak in blood flow that lasted approximately 90 s.

In spite of randomisation and blinding there was a tendency towards higher levels of cortical cerebral blood flow during CPR before intervention in the group later treated with a continuous infusion of adrenaline. This was adjusted for by covariance analysis, using the blood flow level before intervention as a covariate, and testing for the difference in least square means (adjusted means) between the two groups.

Following ROSC, there was an immediate peak in cortical cerebral blood flow in both study groups (Fig. 4). The mean cortical cerebral blood flow increased to about 250% of the baseline level in the continuous group and to about 115% of the baseline level in the bolus group. Maximum blood flow occurred 10–15 min after ROSC and stayed above the baseline level for approximately 60 min in the continuous group and 15 min in the bolus group. However, there was no significant difference between the two study groups in mean cortical cerebral blood flow when analysing the whole 4-h observation period.

Due to technical difficulties, Laser–Doppler flowmetry data were not obtainable in three animals during CPR (two continuous and one bolus) and three animals after ROSC (one continuous and two bolus).

3.2. Jugular bulb oxygen saturation

There was no difference in jugular bulb oxygen saturation between the two groups during CPR or after ROSC (Table 1). Similar changes over time in jugular saturation were observed in both study groups. During CPR, cerebral oxygen extraction was extremely high, with jugular saturation at about one third of baseline values. Five minutes after ROSC, jugular saturation was slightly higher than baseline. After that jugular saturation decreased, with the lowest saturation 30 min after

![Fig. 2. Mean levels of cortical cerebral blood flow during CPR and adrenaline intervention, measured by continuous Laser–Doppler flowmetry. The blood flow is presented as a fraction of the baseline flow level before adrenaline intervention during CPR. Correction is made for differences in mean levels of cortical cerebral blood flow between the treatment groups before adrenaline administration started. Cerebral blood flow during CPR without adrenaline intervention is not shown in the figure, (n = 21).](image-url)
ROSC. This was followed by a gradual increase that reached baseline values 2–3 h after ROSC.

**3.3. Oxidative injury as determined by plasma 8-iso-PGF$_{2\alpha}$**

In both groups there was an increase in jugular bulb plasma concentration of 8-iso-PGF$_{2\alpha}$ to a maximum level three to four times higher than baseline (Table 1). Peak values occurred 5 min after ROSC. This was followed by a gradual decrease in jugular 8-iso-PGF$_{2\alpha}$ that reached baseline at about 3 h after ROSC. There was no difference in jugular bulb plasma concentration of 8-iso-PGF$_{2\alpha}$ between the two groups.

**3.4. Coronary perfusion pressure**

There was no difference in coronary perfusion pressure between the study groups during CPR (Fig. 5). Continuous adrenaline infusion seemed to create less fluctuation in coronary perfusion pressure, while repeated bolus doses resulted in peak values 1 min after administration.

![Graph of cerebral blood flow during CPR and after ROSC](image)

Fig. 3. Cortical cerebral blood flow during CPR before adrenaline intervention (2 min) and while administering adrenaline (7 min). The blood flow is presented as a fraction of baseline flow level. Mean levels derived from the area under the curve are presented for each animal before and during administration of adrenaline. The variation is shown with a box and whisker plot. The box extends from the first to the third quartile and the whiskers represent the range. The horizontal line in the box represents the median. The marker (+) represents the mean, ($n = 21$).

![Graph of mean levels of cortical cerebral blood flow after ROSC](image)

Fig. 4. Mean levels of cortical cerebral blood flow after ROSC measured by continuous Laser–Doppler flowmetry. The blood flow is presented as a fraction of baseline flow level, ($n = 21$).
Table 1
Levels of 8-iso-PGF$_2\alpha$ and oxygen saturation in jugular bulb plasma at baseline, during cardiac arrest and after ROSC

<table>
<thead>
<tr>
<th></th>
<th>8-iso-PGF$_2\alpha$ (pmol/l)</th>
<th>Jugular oxygen saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.D.) n</td>
<td>Mean (S.D.) n</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus</td>
<td>24.6 (11.3) 12</td>
<td>70.2 (12.8) 12</td>
</tr>
<tr>
<td>Cont</td>
<td>31.4 (14.5) 12</td>
<td>74.8 (12.4) 12</td>
</tr>
<tr>
<td><strong>7 min after cardiac arrest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus</td>
<td>24.8 (9.7) 12</td>
<td>74.8 (12.4) 12</td>
</tr>
<tr>
<td>Cont</td>
<td>29.0 (11.1) 12</td>
<td>74.8 (12.4) 12</td>
</tr>
<tr>
<td><strong>30 min after cardiac arrest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus</td>
<td>22.5 (12.0) 12</td>
<td>73.8 (12.4) 12</td>
</tr>
<tr>
<td>Cont</td>
<td>31.3 (17.2) 12</td>
<td>73.8 (12.4) 12</td>
</tr>
</tbody>
</table>

4. Discussion

In this experimental model, a continuous infusion of adrenaline generated a higher mean level of cortical cerebral blood flow during CPR as compared to intermittent bolus doses.

Substantial research has been done in order to determine the optimal dose of adrenaline for bolus administration during CPR. However, irrespectively of the amount administered as a bolus dose, the increase in cerebral blood flow generated is dissipated after 2 min [8]. Therefore, the current guidelines with bolus administration of adrenaline every 3–5 min seem inappropriate [1]. In the present study, we wanted to overcome the short effect duration of a bolus injection by administering adrenaline continuously. The rationale for the chosen dose of continuous adrenaline was based on a study where different doses of continuous infusion of adrenaline were compared demonstrating that 10 µg/kg min of adrenaline was needed to achieve optimal myocardial and cerebral blood flow [7]. In the bolus group, we preferred to give what is considered as standard-dose of adrenaline (20 µg/kg). Bolus doses were administrated every third minute, which is the shortest time interval presently recommended [1]. If we had given the same total amount of adrenaline to both study groups the continuous dose would have been 5.7 µg/kg min. According to Berkowitz et al. [7] this could have been an insufficient dose for continuous administration.

In the present study, bolus administration generated an increase in cortical cerebral blood flow that peaked after 1 min and lasted less than 2 min. In an earlier study by Gedeborg et al., the same pattern was seen in cortical cerebral blood flow during CPR after bolus doses. [8]. This was valid irrespectively if standard dose (20 µg/kg) or high-dose (200 µg/kg) was given. This confirms that intermittent administration has a very short duration of action on cortical cerebral blood flow during CPR. These findings support the idea of administering adrenaline continuously during CPR.

Another possible advantage with continuous administration during CPR is that adrenaline actually will be given in recommended doses. Cardiac arrest is a stressful situation for laymen and hospital staff involved. It is probable that staff members can easily fail to give recommended doses every 3–5 min [1]. If this is the case, bolus doses of adrenaline will be distributed unevenly, and sometimes at long time intervals, providing little beneficial effect on vital organ blood flow during CPR. Pumps for drug administration are easy to handle and should not cause any substantial delay. A continuous infusion could guarantee that adrenaline would be administered during the whole resuscitation period.

Following ROSC there was a period of cerebral hyperperfusion in both study groups that peaked after approximately 15 min. This was most pronounced in the group receiving continuous adrenaline. The cortical cerebral blood flow tended to be higher in the continuous group 3 h following ROSC. However, the inter-individual variation was great, and there was no significant difference in cortical cerebral blood flow between the study groups when comparing the whole 4-h observation period. Regarding the cortical cerebral blood flow after ROSC, there seems to be a difference between the groups within the first hour. However, testing this hypothesis requires a separate study. Jugular venous saturation, representing global cerebral oxygen extraction, consistently tended to be higher in the group receiving continuous adrenaline. However, as with cerebral blood flow, the inter-individual variation was
great and there was no significant difference neither during CPR nor after ROSC. In contrast to cortical cerebral blood flow, there was no difference in coronary perfusion pressure during CPR.

In the present study, there was no difference between the study groups in cerebral oxidative injury, as measured by 8-iso-PGF2α concentration in jugular bulb plasma, when comparing the whole 4-h observation period. However, during the first hour after ROSC there was a tendency towards lower plasma levels of 8-iso-PGF2α in the group that received continuous adrenaline. This could be a result of a greater oxygen supply to the brain as a consequence of higher cerebral blood flow during CPR when administering adrenaline continuously. In an earlier study, a relationship was demonstrated between cerebral ischaemia during cardiac arrest and CPR and the oxidative injury after ROSC as measured by analysing 8-iso-PGF2α in the jugular bulb in the group that received continuous adrenaline. This longer the cardiac arrest lasted, the greater the magnitude and duration of the increased values of 8-iso-PGF2α. As in the former study, with the same duration of cardiac arrest, we found a similar pattern in postresuscitation levels of 8-iso-PGF2α. In both studies, levels of 8-iso-PGF2α in the jugular bulb plasma peaked 5 min after ROSC, with a magnitude about 4 × greater than baseline values. The increased values of 8-iso-PGF2α lasted for about 2–3 h in both studies. Thus, the levels of 8-iso-PGF2α in the jugular bulb plasma in the present study corroborate findings in our earlier study [14] and provide further evidence of the involvement of cerebral oxidative injury during CPR and after ROSC.

Laser-Doppler flowmetry is a highly suitable method for continuous measurement of cortical surface blood flow in the brain. However, the technique only allows measurement of blood flow in a small volume of the brain. In the present study, we therefore combined regional measurement of blood flow with analysis of oxygen saturation in blood from the jugular bulb, an indicator of global cerebral oxygenation.

The apparent difference between groups in cortical cerebral blood flow before intervention with adrenaline occurred in spite of careful randomisation and blinding, and was therefore most probably due to chance alone. Covariance analysis was used in order to adjust for the difference in pre-intervention blood flow levels. This caused the difference seen in cortical cerebral blood flow levels after intervention to be substantially reduced, but it still remained statistically significant. These conditions illustrate the need for strict attention to methodological issues and careful statistical evaluation of data even in this type of carefully controlled laboratory experiment.

In conclusion, continuously administered adrenaline (10 μg/kg min) creates an increase in cortical cerebral blood flow during CPR as compared to intermittent bolus doses (20 μg/kg every third minute). The probable explanation for this is that bolus doses of adrenaline have a short duration of action that results in repeated intervals during CPR with little or no beneficial effects on cortical cerebral blood flow. Continuously administered adrenaline appears to result in a more sustained increase in cortical cerebral blood flow during CPR. Thus, the presently recommended way of administering adrenaline during CPR might not be optimal for the
cerebral circulation. Further studies are needed to evaluate the effects of continuous adrenaline on survival and neurological outcome.

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