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Brain metabolism during cardiopulmonary resuscitation assessed with microdialysis

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Abstract

Background and Purpose: Microdialysis is an established tool to analyse tissue biochemistry, but the value of this technique to monitor cardiopulmonary resuscitation (CPR) effects on cerebral metabolism is unknown. The purpose of this study was to assess the effects of active-compression-decompression (ACD) CPR in combination with an inspiratory threshold valve (ITV) (= experimental CPR) vs. standard CPR on cerebral metabolism measured with microdialysis. *Methods:* Fourteen domestic pigs were surfaced-cooled to a body core temperature of 26 °C and ventricular fibrillation was induced, followed by 10 min of untreated cardiac arrest; and subsequently, standard ($n = 7$) CPR vs. experimental ($n = 7$) CPR. After 8 min of CPR, all animals received 0.4 U/kg vasopressin IV, and CPR was maintained for an additional 10 min in each group; defibrillation was attempted after a total of 28 min of cardiac arrest, including 18 min of CPR. *Results:* In the standard CPR group, microdialysis measurements showed a 13-fold increase of the lactate–pyruvate ratio from 7.2 ± 1.3 to 95.5 ± 15.4 until the end of CPR ($P < 0.01$), followed by a further increase up to 138 ± 32 during the postresuscitation period. The experimental group developed a sixfold increase of the lactate–pyruvate ratio from 7.1 ± 2.0 to 51.1 ± 8.7 ($P < 0.05$), and a continuous decrease after vasopressin. In the standard resuscitated group, but not during experimental CPR, a significant increase of cerebral glucose levels from 0.6 ± 0.1 to 2.6 ± 0.5 mM was measured ($P < 0.01$). *Conclusion:* Using the technique of microdialysis we were able to measure changes of brain biochemistry during and after the very special situation of hypothermic cardiopulmonary arrest. Experimental CPR improved the lactate–pyruvate ratio, and glucose metabolism.

Keywords: Cardiopulmonary resuscitation; Active compression decompression; Metabolism; Brain ischaemia; Catheter

Resumo

Contexto: A microdiálise é um método de análise da bioquímica tecidular aceite, mas o valor desta técnica para monitorizar os efeitos da reanimação cardio-pulmonar (CPR) no metabolismo cerebral é desconhecido. O objectivo deste estudo foi avaliar os efeitos da CPR por compressão-descompressão activa (ACD) em combinação com uma válvula de nível inspiratório (ITV), CPR experimental vs CPR standard, no metabolismo cerebral avaliado com microdiálise. *Métodos*: Arrefeceram-se catorze porcos domésticos até uma temperatura corporal central de 26 °C induziu-se fibrilhação ventricular, seguida de 10 min de paragem cardíaca não tratada; subsequentemente, foi realizada CPR standard ($n = 7$) vs. CPR experimental ($n = 7$). Depois de 8 min de CPR, todos os animais receberam 0.4 U/Kg de vasopressina IV e a CPR foi mantida por mais 10 min em cada grupo; foi tentada desfibrilhação após um total de 28 min de paragem cardíaca, incluindo 18 min de CPR. *Resultados*: No grupo de CPR standard, as medições por microdiálise mostraram um aumento de 13 vezes da razão lactato-piruvato de 7.2 ± 1.3 para 95.5 ± 15.4, até ao final da CPR ($P < 0.01$), seguido de uma aumento adicional até 138 ± 32 no período pós-reanimação. O grupo experimental desenvolveu um aumento de 6 vezes da razão lactato-piruvato, de 7.1 ± 2.0 para 51.1 ± 8.7 ($P < 0.05$), e um aumento contínuo após vasopressina. No grupo de

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reanimação standard, mas não durante a CPR experimental, foi medido um aumento significativo dos níveis de glicose cerebral, de 0.6 ± 0.1 para 2.6 v 0.5 mM ($P < 0.01$). *Conclusões*: Através da técnica da microdiálise foi possível medirmos alterações na bioquímica cerebral durante e após a situação muito especial de paragem cardiopulmonar por hipotermia. A CPR experimental aumentou a razão lactato-piruvato e o metabolismo da glicose.

Palavras chave: Ressuscitação cardiopulmonar; Compressão-descompressão activa; Metabolismo; Isquemia cerebral; Cateter

Resumen

Antecedentes y propósito: La microdiálisis es una herramienta establecida para analizar la bioquímica de los tejidos, pero se desconoce el valor de esta técnica para monitorizar los efectos de la reanimación cardiopulmonar (CPR) sobre el metabolismo cerebral. El propósito de este estudio fue evaluar los efectos de la reanimación cardiopulmonar(CPR) por compresión y descompresión activa (ACD) en combinación con una válvula de umbral inspiratorio (ITV) (= reanimación experimental) vs. CPR estándar, sobre el metabolismo cerebral medido con microdiálisis. *Métodos*: Catorce cerdos domésticos fueron sometidos a enfriamiento superficial hasta una temperatura corporal de 26 ° C y se indujo fibrilación ventricular, seguido de 10 minutos de paro cardíaco no tratado; y luego se realizó, CPR estándar ($n = 7$) vs. CPR experimental ($n = 7$). Después de 8 minutos de CPR, todos los animales recibieron vasopresina intravenosa 0.4 U/kg, se mantuvo CPR por 10 minutos adicionales en cada grupo; y se intentó la desfibrilación después de un total de 28 minutos de paro cardíaco, incluyendo 18 minutos de CPR. *Resultados*: En el grupo de CPR estándar, las mediciones de microdiálisis mostraron un aumento de 13 veces en la relación lactato-piruvato de $7.2 + 1.3$ a $95.5 + 15.4$ hasta el final del CPR ($P < 0.01$), seguido por un ulterior aumento hasta $138 + 32$ durante el período de post resucitación. El grupo experimental desarrolló un aumento de 9 veces en la relación lactato – piruvato desde $7.1 + 2.0$ hasta $51.1 + 8.7$ ($P < 0.05$), y una disminución continua después de la vasopresina. En el grupo de resucitación estándar se midió un aumento significativo de los niveles de glucosa desde 0.6 ± 0.1 hasta 2.6 ± 0.5 mM ($P < 0.01$), no así durante la resucitación experimental. *Conclusión*: Usando la técnica de microdiálisis pudimos medir los cambios en la bioquímica cerebral durante y después de la muy especial situación de paro cardiopulmonar hipotérmico. La reanimación cardiopulmonar experimental mejoró la relación lactato piruvato, y el metabolismo de glucosa.

Palabras clave: Reanimación cardiopulmonar; Compresión descompresión activa; Metabolismo; Isquemia cerebral; Catéter

1. Introduction

Monitoring of cardiopulmonary resuscitation (CPR) efforts has been traditionally based on variables such as coronary perfusion pressure [1], end-tidal carbon dioxide [2], and ventricular fibrillation mean frequency [3]. While arterio-venous blood gas gradients may be a surrogate for an estimated regional perfusion, they do not necessarily imply a certain organ function. For example, similar to the theory of a stunned myocardium, it has been speculated that the brain may be prone to metabolic stunning during CPR [4]. Accordingly, traditional monitoring tools such as electroencephalography, transcranial doppler ultrasonography and jugular bulb venous saturation possibly could be supplemented by microdialysis to closely monitor brain metabolism during CPR [5–7].

Microdialysis is a technique that can be used to sample the interstitial fluid of nearly every organ for biochemical measurements. This technique is employed increasingly to monitor brain metabolism, especially in neurosurgical studies [8–10]. Unfortunately, it is not known whether data of patients undergoing brain surgery with beating hearts can be extrapolated to the cardiac arrest setting with ongoing CPR. Moreover, hypothermic CPR is an even greater challenge since it reflects a profoundly decreased metabolism, and low perfusion pressure during CPR [11]. Thus, if microdialysis is as valuable in hypothermic CPR as in neurosurgical patients, it may be a beneficial tool to assess regional organ metabolism during CPR.

The purpose of the present study was to perform microdialysis during CPR in an established animal model. Moreover, since active-compression-decompression CPR in combination with an inspiratory threshold valve (experimental CPR) may increase oxygen delivery during normothermic CPR [12,13] and cerebral oxygen consumption during hypothermia may be significantly decreased, benefits of this technique may be even greater during hypothermic CPR. Our hypothesis was that there would be no differences in metabolism variables in pigs receiving experimental vs. standard CPR.

2. Materials and methods

This investigation was approved by the Austrian Federal Animal Investigational Committee, and the animals were managed in accordance to guidelines of the American Physiology Society, and institutional guidelines. Our animal facilities meet the standards of the American Association for Accreditation of Labora-

tory Animal Care. This study was performed according to the Utstein-style guidelines [14] on 14 adult pigs of either gender weighing 30–40 kg. Anaesthesia was used in all surgical interventions, all unnecessary suffering was avoided, and research was terminated if unnecessary pain or fear resulted. All pigs were fasted overnight, but had free access to water. One hour before surgery, the pigs were premedicated with azaperone (neuroleptic agent), 4 mg/kg IM and atropine, 0.1 mg/kg IM. Anaesthesia was induced with a bolus dose of ketamine (20 mg/kg IM), propofol (1–2 mg/kg IV), and piritramid (30 mg IV) given via an ear vein [15]. The animals were placed on a U-shaped board, and their trachea was intubated during spontaneous respiration. Thereafter, mechanical ventilation was performed with a volume-controlled ventilator (Draeger EV-A, Luebeck, Germany) with 35% Oxygen at 15 breaths per minute, and with a tidal volume adjusted to achieve normocapnia ($PaCO_2$ 35–40 mm Hg). Anaesthesia was maintained with a continuous infusion of propofol (6–8 mg/kg/h); muscle relaxation was provided by a continuous infusion of pancuronium (0.2 mg/kg/h). Depth of anaesthesia was adjusted according to blood pressure, heart rate, and electroencephalographic display (delta, theta, alfa and beta and electroencephalographic power and 95% spectral edge frequency; Neurotrac, Engström, Munich, Germany). If these variables indicated a reduced depth of anaesthesia, additional propofol and piritramid was given. Ringer's solution (6 ml/kg/h) was infused during the preparation phase to replace fluid and blood loss; cardiac rhythm was monitored using a standard lead II ECG. One 7F saline-filled catheter was advanced via femoral cutdown into the right atrium for measuring of right atrial pressure, and for drug administration; another 7F catheter was advanced via femoral cutdown into the thoracic aorta for measurement of aortic blood pressure, and withdrawal of arterial blood samples. Before trepanation, 5 ml local anaesthetic (lidocaine 2%) was infiltrated into the skin overlying the skull between the eyes to provide additional anaesthesia. A burr hole of 1 cm in diameter was drilled into the skull and the dura mater incised with a scalpel. Then a CMA 70 microdialysis catheter (CMA/Microdialysis, Stockholm, Sweden) was introduced through this tunnel into the right frontal cortex. A unique slit cannula introducer was used. After removing of the introducer the CMA 70 catheter remained in situ. A control catheter was placed into the gluteal muscle.

The technique of microdialysis [16,17] is based on sampling interstitial fluid via a doublelumen probe with an integrated semipermeable membrane. In our experiment, the inlet of the microdialysis catheter was constantly perfused with lactate-free Ringer's solution at a flow rate of 2 μl/min. This enabled a recovery rate of nearly 50%. The microvials were changed at timed intervals (cooling period: 30 min, cardiac arrest: 5 min, CPR until vasopressin: 4 min, after vasopressin and post resuscitation: 5 min). Interstitial fluid was stored at −30 °C for later serial analysis.

2.1. Experimental protocol

After preparation and instrumentation, the animals were placed on a bed of crushed ice and the entire body was covered with ice, until a body core temperature of 26 °C (rectal) was achieved. The animals were paralyzed with 8 mg/kg pancuronium. In addition 15 mg piritramid was given, and 5000 U heparin were administered intravenously to prevent intracardiac clot formation. A 50-Hz, 60-V alternating current was then applied via two subcutaneous needle electrodes in order to induce ventricular fibrillation. Cardiac arrest was determined by a sudden decrease in aortic blood pressure to hydrostatic pressure, and the ECG showing ventricular fibrillation; ventilation was stopped at this point. After 10 min of untreated ventricular fibrillation, closed-chest CPR at a rate of 100/min was started performing standard CPR ($n = 7$) or experimental CPR ($n = 7$). Mechanical ventilation was resumed with the same setting as before induction of cardiac arrest. After 8 min of CPR, 0.4 U/kg vasopressin IV was administered in all animals. All drugs were diluted to 10 ml normal saline, and subsequently injected to the right atrium; followed by a 20-ml saline flush. After 28 min of cardiac arrest, including 18 min of CPR, up to three monophasic countershocks were administered with an energy of 100, 150, and 200 J. The ECG analysis after the defibrillations took not more than 10 s. In case of asystole, pulsless electrical activity or refractory ventricular fibrillation after defibrillation, CPR was resumed, followed by up to three defibrillation attempts. If the animals did not have return of spontaneous circulation, the experiment was terminated. After finishing the experiment, euthanasia was induced with an overdose of propofol, fentanyl and potassium chloride; all pigs were then autopsied to verify correct positioning of the catheters, damage to the rib cage, and internal organs.

2.2. Statistical analysis

The results are presented as mean ± SEM for all measuring points. Differences between the measurements and baseline were assessed by a Friedmans ANOVA followed by a Wilcoxon–Wilcox-test. The statistical comparison between the two groups was accomplished using a non-parametric Mann–Whithney U Test. A P value < 0.05 was considered statistically significant.

3. Results

A significant decrease in mean arterial blood pressure was observed during the cooling process in both groups. During and after CPR, the experimental group had significantly higher mean arterial blood pressure values (Fig. 1). Return of spontaneous circulation rates were comparable in the standard (3 of 7) and in the experimental (4 of 7) CPR group.

Cerebral lactate values increased significantly during CPR in both groups ($P < 0.05$), followed by a slight decrease thereafter (Fig. 2). A significant decrease of cerebral pyruvate was measured during cardiac arrest, and the beginning of CPR in each group ($P < 0.05$). In the experimental group, but not in the standard group, pyruvate increased until the end of CPR, respectively thereafter ($P < 0.05$) (Fig. 3). The standard CPR group showed a 13-fold increase in the lactate–pyruvate-ratio from 7.2 ± 1.3 to 95.5 ± 15.4 during CPR ($P < 0.01$), followed by a further increase. The experimental group developed only a sixfold increase in the lactate–pyruvate-ratio from initial 7.1 ± 2.0 to 51.1 ± 8.7 until the end of CPR ($P < 0.05$). After the administration of vasopressin the lactate–pyruvate-ratio remained at nearly the same level (Fig. 4). In the gluteal muscle, the standard CPR group developed a significantly higher increase in the lactate–pyruvate-ratio until the end of the experiment. In the standard CPR animals, we initially observed a significantly higher increase in cerebral glucose from 0.7 ± 0.2 at baseline to 2.4 ± 0.8 during CPR; after vasopressin, however, we observed a steep decline, followed by another continuous increase. The experimental CPR animals showed no essential changes in either cerebral or muscular glucose metabolism during the entire observation period (Fig. 5).

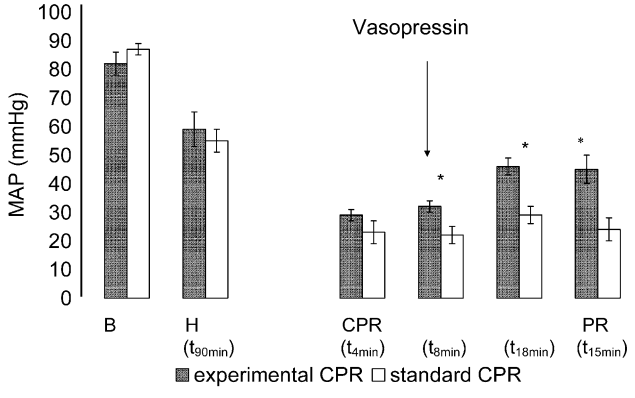

Fig. 1. Mean ± SEM arterial blood pressure throughout the experiment. *$P < 0.05$ standard vs. experimental CPR. B, baseline; H, hypothermia; CA, cardiac arrest; PR, postresuscitation period.

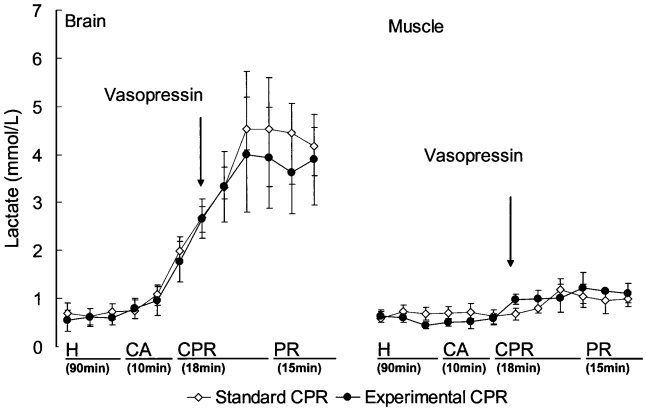

Fig. 2. Mean ± SEM interstitial lactate before, during, and after CPR in the interstitial fluid of the brain, and gluteal muscle. *$P < 0.05$ standard vs. experimental CPR. H, hypothermia; CA, cardiac arrest, PR, postresuscitation period.

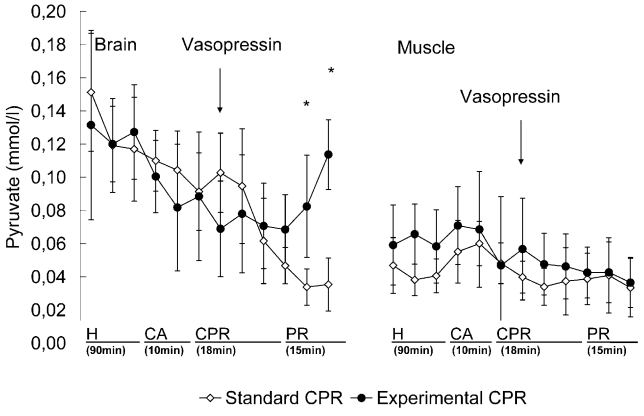

Fig. 3. Mean ± SEM interstitial pyruvate before, during, and after CPR in the interstitial fluid of the brain, and gluteal muscle. *$P < 0.05$ standard vs. experimental CPR. H, hypothermia; CA, cardiac arrest; PR, postresuscitation period.

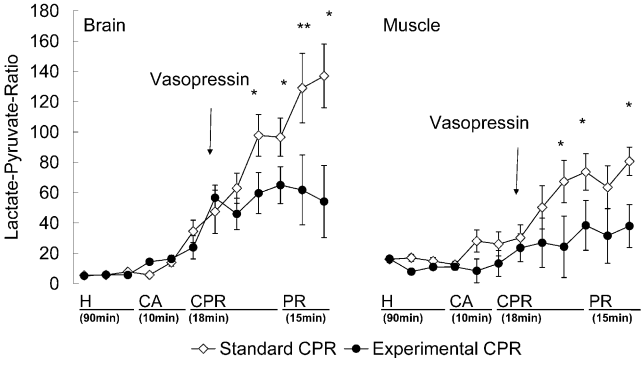

Fig. 4. Mean ± SEM, interstitial lactate–pyruvate-ratio of the brain, and gluteal muscle before, during, and after CPR. *$P < 0.05$ and **$P < 0.01$ standard vs. experimental CPR. H, hypothermia; CA, cardiac arrest; PR, postresuscitation period.

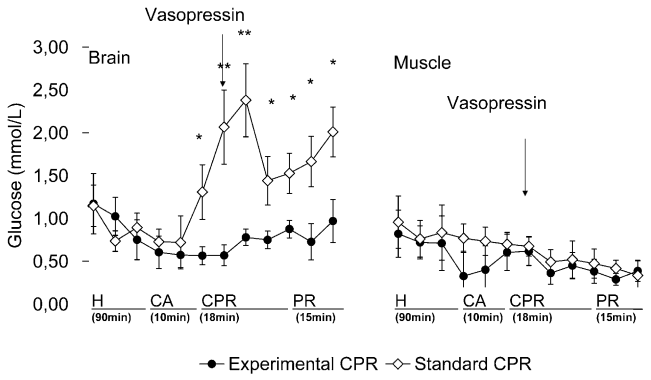

Fig. 5. Mean ± SEM interstitial glucose before, during and after CPR in the interstitial fluid of the brain, and gluteal muscle. $^{*}P < 0.05$ standard vs. experimental CPR. H, hypothermia; CA, cardiac arrest; PR, postresuscitation period.

4. Discussion

When comparing experimental vs. standard CPR, we showed that microdialysis was a sensitive technique to detect differences in brain metabolism even during a low flow state such as CPR. Moreover, microdialysis was able to reveal changes in brain metabolism variables within a few minutes, indicating that this approach may be valuable to indirectly assess brain perfusion. The present experiment was performed in an established porcine model to ensure that confounding variables were kept at a minimum level. Also, the duration and the degree of hypothermia have been shown in previous models to be clinically relevant [11]. Further, trepanation of the skull was carefully closed after instrumentation of microdialysis probes in order to ensure that boyland's law is applicable, as done before [18].

In resuscitation medicine, the dogma has been for many years that no vasopressor should be administrated when temperature is $< 30\ ^{\circ}C$ due to the fear of profoundly decreased metabolism of advanced cardiac life support drugs that may lead to toxic effects, or that vasopressors may be simply ineffective. In several experiments we have shown that our laboratory data is in strong contrast to these opinions [11,19,20]. The present data, in fact, reveals that even during profound hypothermia, significant changes in metabolism of both brain and muscle as reference organ are present, and detectable. In both CPR groups, the lactate–pyruvate ratio between onset of cardiac arrest and drug administration 8 min later revealed a sixfold increase in the brain, and a twofold increase in the muscle. After vasopressin, in the experimental but not in the standard CPR group, the lactate–pyruvate ratio remained stable at a level of ~ 60 followed by a slight decrease thereafter. This indicates that the triple approach consisting of ACD + ITV + vasopressin may have a beneficial effect on cerebral oxygenation. It is noteworthy, however, that cerebral lactate levels were comparable between groups throughout the experiment; since the lactate–pyruvate ratio was significantly different in the brain between groups. It is suggested that brain metabolism was not stunned, but very active. Thus, as suggested earlier by other colleagues such as Safar, resuscitation of the brain may start immediately upon initiating CPR [21,22]. In contrast to the lactate–pyruvate-ratio, the two groups showed differences of the cerebral glucose measurements immediately after onset of ventricular fibrillation. Thus, it may be possible that the $\sim 35\%$ greater mean arterial blood pressure in experimental vs. standard CPR pigs maintained homeostasis; and therefore, guaranteed better brain metabolism during severe hypothermia. Another theory, however, is that a fundamental endogenous catecholamine discharge due to insufficient vital organ perfusion in the standard CPR pigs was the underlying reason for increased glucose levels. In regard to glucose levels, and therefore metabolism in the brain, differences were especially prominent; this may explain why increased glucose levels during and after CPR may be a surrogate for impaired neurological outcome after CPR [23].

In an animal experiment of CPR Shaffner and colleagues assessed cerebral energy metabolism using a non invasive magnet resonance spectroscopy (MRS) [24]. They described fundamental changes of adenosine triphosphate levels during the experiment comparing dogs resuscitated with a cerebral perfusion pressure (CPP) of 25, respectively 35 mmHg after different arrest times. Those animals with a CPP of 35 mmHg during CPR showed a significantly better ATP recovery. Using the technique of microdialysis it is possible to analyse ATP metabolism. Thus it might be interesting to compare these two different metabolic monitoring tools. Instead of vasopressin, adrenaline (epinephrine) was given during their normothermic CPR experiment.

In our animal experiment we were interested in those biochemical variables, which are normally recorded in critical care practice and available as bedside data (CMA 600 Analyser/CMA, Solna, Sweden). At present intravenous microdialysis does not exist. In our study we did not compare the cerebral microdialysis with systemic blood gas measurements. Moreover, we took the gluteal muscle for reference measurements and inserted a second CMA 70 microdialysis catheter there. It was the aim to compare two regions using the same technique with identical perfusion rates and the same measurement intervals. In the microdialysis literature this procedure is very common. In a lot of studies the subcutaneous or the muscular space is taken for reference measurements [8–10].

Some limitations should be noted. First, young and healthy pigs free of atherosclerotic disease were employed in the study. Second, different effects of arginine vasopressin as in our study may be observed in pigs with lysine vasopressin receptors in comparison with humans

who have arginine vasopressin receptors. Third, we did not measure regional perfusion, which impedes exact calculation of regional oxygen delivery and consumption. We only compared the mean arterial blood pressure with the cerebral microdialysis. Detailed haemodynamic measurements (cardiac index, vascular resistance, cerebral blood flow etc.) are certainly useful for a better understanding of the cerebral microdialysis results, and should have been performed.

In conclusion, microdialysis effectively detected changes in brain metabolism during cardiopulmonary arrest, CPR, and the postresuscitation period. The experimental CPR improved the lactate–pyruvate ratio and glucose levels in comparison with standard CPR.

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