

Neuroprotective effect of selective antegrade cerebral perfusion during prolonged deep hypothermic circulatory arrest: Cerebral metabolism evidence in a pig model

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ABSTRACT

Objective: The aim of this study was to elucidate the mechanism of cerebral injury and to evaluate selective antegrade cerebral perfusion (SACP) as a superior neuroprotective strategy for prolonged deep hypothermic circulatory arrest (DHCA).

Methods: Twelve pigs (6–8-week old) were randomly assigned to DHCA alone (n=6) and DHCA with SACP (n=6) at 18°C for 80 min groups. Serum S100 was determined using an immunoassay analyzer. The concentrations of cerebral dialysate glucose, lactate, pyruvate, glycerol, and glutamate were measured using a microdialysis analyzer.

Results: Compared with a peak at T4 (after 60 min of rewarming) in the DHCA group, the serum S100 in the SACP group was significantly lower throughout the study. The DHCA group was susceptible to significant increases in the levels of lactate, glycerol, and glutamate and the ratio of lactate/pyruvate as well as decreases in the level of glucose. These microdialysis variables showed only minor changes in the SACP group. There was a positive correlation between cerebral lactate and intracranial pressure during reperfusion in the DHCA group. However, the apoptosis index and C-FOS protein levels were lower in the SACP group.

Conclusion: Metabolic dysfunction is involved in the mechanism of cerebral injury. SACP is a superior neuroprotective strategy for both mild and prolonged DHCA. (*Anatol J Cardiol* 2018; 19: 2-10)

Keywords: DHCA, SACP, cerebral injury, neuroprotective strategy, microdialysis, metabolism

Introduction

With the remarkable advances in surgical skills, anesthesia, and intensive care, deep hypothermic circulatory arrest (DHCA), which reduces metabolic demand and oxygen consumption, has effectively prolonged the tolerated duration of circulatory arrest and reduced complications and mortality to an acceptable level (1-3). On the other hand, DHCA interrupts blood flow and inevitably leads to neuropsychopathic complications, such as seizures, language delays, coagulopathy, respiratory and renal failure, and an increased inflammatory response (4), which can be one of the most significant risk factors influencing a patient's prognosis. DHCA is considered to play an important role in neurological morbidity (5).

Because of advances in techniques, treatment of DHCA with retrograde cerebral perfusion (RCP), antegrade cerebral perfu-

sion, and selective antegrade cerebral perfusion (SACP) has become the chief method to protect patients from cerebral injury by providing adequate cerebral blood flow (6). It is already known that RCP can prolong safe arrest durations but may not improve outcomes (7). Presently, SACP is dominantly used in operations involving arch reconstruction. Despite its relative disadvantages, SACP still has considerable advantages, including the consistency in normal physiology, potential benefits to prolong the tolerated duration of circulatory arrest, and ameliorating effects on brain cooling (8-10). Nevertheless, there is continual controversy over the details of SACP practice, including the optimal perfusate temperature, site of cannulation, choice of bilateral or unilateral cerebral perfusion, type of blood gas management when cooling and rewarming, and cerebral perfusion flow and pressure levels (11, 12). The maximum DHCA intervals are about 80 min for prolonged

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Accepted Date: 23.10.2017 **Available Online Date:** 03.01.2018

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DOI:10.14744/AnatolJCardiol.2017.7946



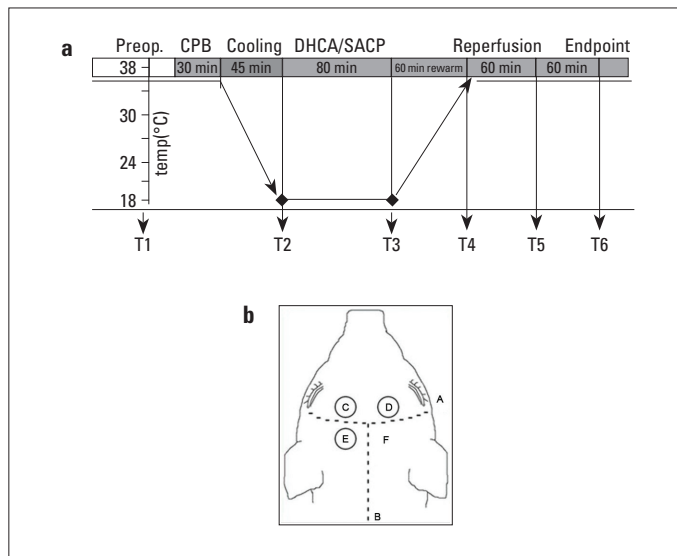


Figure 1. (a) Experimental protocol schematic diagram for this study: T1. Baseline, at a cerebral temperature of 36°C, just before cooling; T2. After 45 min of cooling, at a nasopharynx/esophagus temperature of 18°C, before DHCA/SACP; T3. After an 80-min DHCA/SACP, before initiation of cardiopulmonary bypass (CPB); T4. after 60 min of rewarming; T5. After 120 min of reperfusion; T6. endpoint, after a 180-min reperfusion. (b) The skull sketch map for placing probes (A for coronal suture; B for sagittal suture; C for ICP; D for temperature; E for microdialysis; F for bregma)

DHCA, and they even reached 100 min in a recent clinical data report (13, 14). Extending the time limit of DHCA beyond this point has been associated with increased risk of adverse neurological outcomes. For this reason, it is clinically necessary to determine which cerebral protection strategy should be adopted preoperatively, particularly for prolonged DHCA. The validity of SACP as a neuroprotective strategy for prolonged DHCA is still undetermined.

Microdialysis is a new type of biological sampling and drug delivering technology, which offers real-time, continuous, and online monitoring of changes in the neurobiological and energy metabolisms that occur after cerebral ischemia, providing a new method to further the understanding of the pathological changes resulting from cerebral ischemia and the related clinical control (15, 16). Accordingly, the aim of this study is to elucidate the mechanism of cerebral injury through metabolism by means of microdialysis applied to a pig model as well as to evaluate the validity of SACP as a neuroprotective strategy for prolonged DHCA.

Methods

Study design

Twelve Wuzhishan miniature pigs aged 6–8 weeks and weighted 9.7–13 kg were used in this experiment. All animal studies had been approved by The Institute Research Medical Ethics Committee of Sun Yat-Sen University. All animals were divided into two groups, the DHCA and SACP groups. Both groups underwent an 80-min DHCA at 18°C, followed by a 180-min reperfusion, including 60 min of rewarming. The SACP group underwent 80 min of SACP during DHCA. The experimental protocol schematic

diagram is shown in Figure 1a. At each time point, blood samples were collected and the physiological, hemodynamic, and intracranial pressure (ICP) parameters were recorded. At the endpoint, all animals were sacrificed, and specimens of the cerebral cortex were harvested.

Anesthesia and preoperative management

The anesthesia, intubation, and establishment of vascular catheters were performed as described previously (17, 18). Then, animals were easily equipped with intracerebral probes. Three 0.8-mm-diameter burr holes were drilled in three quadrants centered in the bregma of the skull with access to the superficial cerebral cortex (Fig. 1b). A CMA70 microdialysis catheter (CMA Microdialysis AB, Solna, Sweden) was inserted 4-mm deep into hole E to collect the dialysate from the cerebral cortex (Fig. 1b). An intraparenchymal microtip pressure catheter (Codman ICP Express, Raynham, MA) was placed 3-mm deep into the cerebral cortex through hole C after puncture of the dura (Fig. 1b). ICP was recorded by connecting the catheter to the transducer of a multichannel physiologic recorder (MP150, BIOPAC Systems, Inc., California, USA), and the recordings were analyzed using the AcqKnowledge system (Version 3.8.1, BIOPAC Systems, Inc). Hole D (Fig. 1b) was devoted to monitoring the cerebral temperature with a microprobe (Licox Integra, Plainsboro, NJ) connected to the transducer of a multichannel physiologic recorder (MP150, BIOPAC Systems, Inc. California, USA).

Surgical procedures and cardiopulmonary bypass

A median sternotomy was performed, and the strings were sutured. Cardiopulmonary bypass (CPB) was performed using two roller pumps for extracorporeal circulation and suction. The extracorporeal circuit and membrane oxygenator were primed (Minimax Plus Oxygenator SK3301, Medtronic Inc, USA) with blood from another piglet, and multiple electrolytes were injected. Heparin (3 mg/100 mL blood; 3 mg/100 mL crystal liquid) was added, the CPB flow was stabilized at 75–80 mL·kg⁻¹·min⁻¹, and the mean systemic perfusion pressure was 50–80 mm Hg.

Deep hypothermic circulatory arrest

DHCA was induced as described previously (17). Animals were systemically cooled for 45 min, and when the body temperature reached 30°C, the ascending aorta was cross clamped and the cardioplegia solution was administered. After the body temperature dropped to 18°C, the roller pumps were switched off. Then, DHCA tests were performed for the next 80 min. Next, the aorta was declamped and the animal returned to a normal body temperature over a 60-min period. When the hemodynamic data of animal became steady after partial perfusion, CPB was stopped. Animals were then sacrificed for tissue harvesting.

Selective antegrade cerebral perfusion

SACP was performed as described previously (17). After reaching the target temperature, we performed aortic cross

clamping and stopped CPB. Passive venous drainage into the blood reservoir was allowed after undergoing DHCA. After 5 min, SACP started via a 6-Fr catheter inserted into the innominate artery for 80 min. The perfusion pressure was stabilized at 40–50 mmHg (10 mL/kg/min). At the end of the DHCA period, the snare on the innominate artery was released, and a complete CPB was gradually restored. Rewarming was performed for next 60 min.

Tissue harvesting

At T6, we opened the skull carefully and removed the frontal cortex quickly. Samples were fixed either in 10% buffer paraformaldehyde solution or 2.5% glutaraldehyde in 0.1 M sodium cacodylate (pH 7.4) at 4°C for 24 h for the following experiments.

Biochemical analysis

The serum S-100 protein (121773001V5, Cobas, Roche) concentration was determined with an immunoassay analyzer (Cobas e 601, Roche) using an electrochemiluminescence immunoassay method.

Transmission electron microscopes

For transmission electron microscopy, after rinsing in a cacodylate solution, the cortex specimens were washed in Sorenson's phosphate buffer and fixed in a 1% osmium tetroxide and 0.1 M cacodylate solution at 4°C for 60 min for the second time, dehydrated in a graded series of ethanol, immersed in propylene oxide, and finally infiltrated and embedded in araldite. Ultrathin sections (40–60 nm) were cut, placed on copper grids (200 mesh), stained with saturated uranyl acetate and lead citrate, and finally examined with an electron microscope (FEI, USA) using a 20 µm objective aperture at an acceleration voltage of 75 kV.

Fluorescence TUNEL

After deparaffinizing in xylene for 5 min, sections were hydrated with 100% ethanol for 3 min and 95% ethanol for 1 min. Sections were incubated with proteinase K (20 µg/mL in 10 mM Tris/HCL, pH 7.4) for 30 min. The incubated sections were then successively added to a TdT Reaction Mixture for 60 min and Hoechst 33258 for 10 min at 37°C in a humidified chamber. Coverslip sections were added on top of a mounting medium. All of the above steps were followed by rinsing in PBS for 2 min. Positive results were confirmed when the nuclear color was stained brown. For quantification of apoptotic cells, a ×10–40 magnification and a Zeiss eyepiece graticule with 100 grids per square were used. Apoptotic neurons were counted in 10 different fields in each region at ×40 magnification using defined areas in the cortex. The investigator who analyzed the TUNEL sections was blinded to the group identity. Apoptotic neurons were expressed as apoptosis index (AI), which was calculated using the equation $AI = \text{apoptotic neurons} / \text{total neurons} \times 100\%$.

Western blot

Total proteins were lysed by RIPA buffer. The protein concentration was assessed by Bradford assay, and proteins were

separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Then, proteins were transferred to nitrocellulose membranes and blocked with 5% nonfat milk for 2 h at room temperature. Subsequently, the membranes were washed with TBST (NaCl, 0.1% Tween-20, Tris) and incubated overnight with primary antibodies at 4°C followed by two washes in TBST. Next, the membranes were incubated with the secondary antibodies for 1 h at room temperature and washed with TBST three times. GAPDH was used as the loading control.

Statistical analysis

All statistical analyses were performed using SPSS 20.0 for Windows (IBM SPSS, USA). Data is expressed as mean ± standard deviation ($\bar{x} \pm SD$). ANOVA and Student's unpaired t-tests were used to evaluate significant differences. Spearman's correlation was used to analyze the correlation between cerebral lactate and ICP. A p-value of <0.05 was considered statistically significant.

Results

Biochemical analysis

Following a slow increase at T2, S100 showed a sudden rise and reached the peak value at T4 ($t=21.12$, $p=0.000$) in the DHCA group. Serum S100 level remained stable throughout the study (Fig. 2a) in the SACP group.

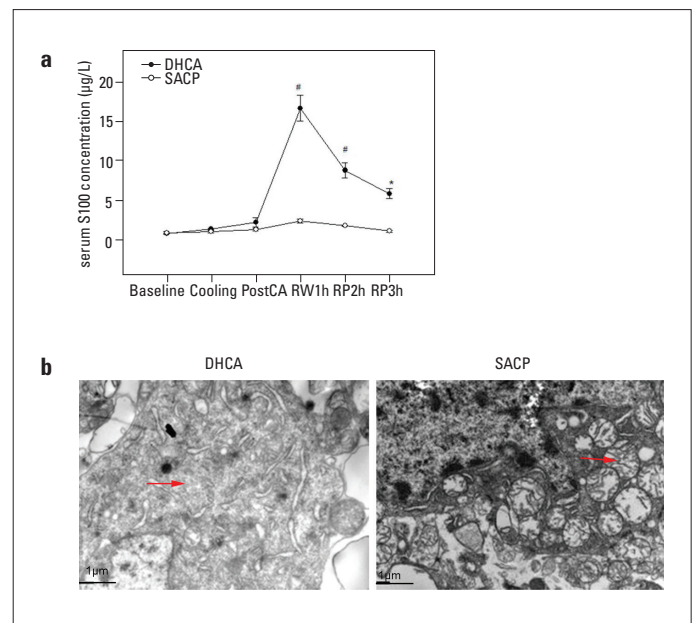


Figure 2. (a) The serum S100 concentration detected by electrochemiluminescence immunoassay (PostCA, after circulatory arrest; RW, re-warm; RP, reperfusion ^{*}, $P<0.05$; [#], $P<0.01$), and the electron micrograph (b) of the cerebral cortex (original magnification, ×13500) of the DHCA and SACP groups. Ultrastructure was rarefaction and disorganization (red arrow), mitochondria distension significant in DHCA group. The ultrastructure was nearly normal despite the moderately distant mitochondria (red arrow) and swollen cytoplasm in the SACP group

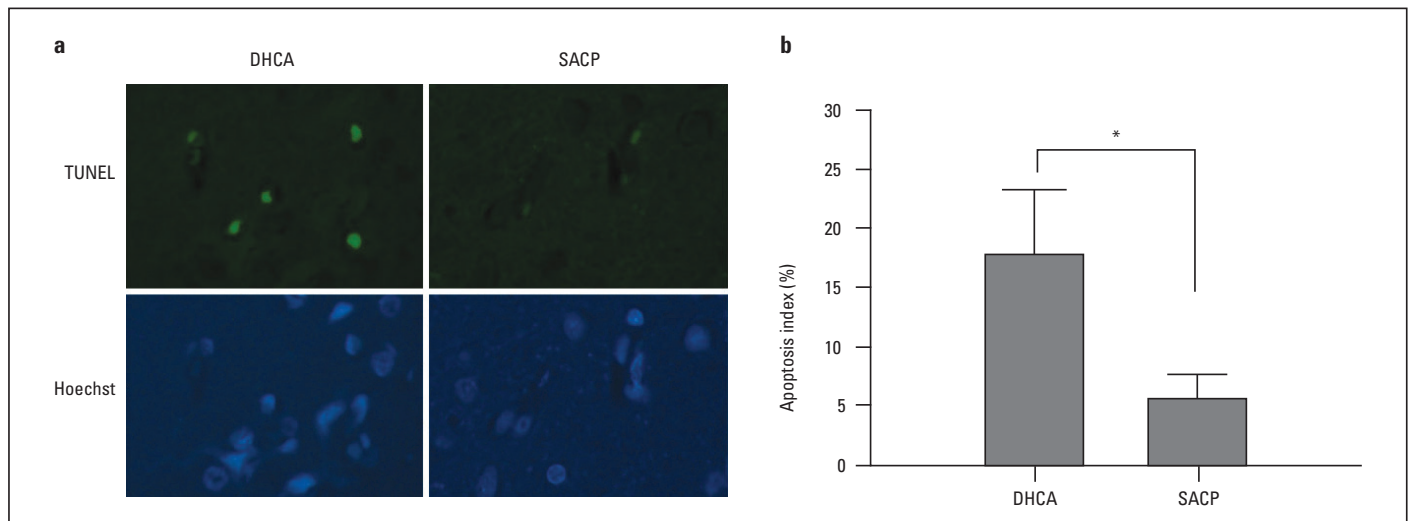


Figure 3. Fluorescence TUNEL staining of the frontal cortex (original magnification, x400). A more positive TUNEL reaction staining was seen in the nuclei of the neurons in the DHCA Group. There was lesser positive TUNEL staining in the SACP group. B is the apoptosis index calculated in the DHCA and SACP groups (17.89±5.35 vs. 9.66±1.97, $t=3.319$, $P=0.02$).

Transmission electron microscope

More severe neuronal damage was observed in the cortexes of the DHCA group (Fig. 2b), including rarefaction and disorganization, nuclei margins and pyknosis, disorganized mitochondria, and even cristae disruptions and amorphous matrix densities. The ultrastructure of the cortex in the SACP group was nearly normal except for the slightly swollen cytoplasm and mitochondria; disrupted crestia were not observed (Fig. 2b).

Fluorescence TUNEL

Compared with the number of positive nuclei in the DHCA cerebral cortexes, there were fewer positive nuclei in the SACP-treated cerebral cortexes (Fig. 3a). The AI of the DHCA group was significantly higher than that of the SACP group (Fig. 3b, 17.89±5.35 vs. 9.66±1.97, $t=3.319$, $p=0.02$).

Intracranial pressure

During circulatory arrest (CA), the ICP level of the DHCA group declined, whereas minor changes were found in that of the SACP group. A statistically significant difference was observed between the two groups ($t=-7.37$, $p=0.001$). The maximum value of ICP in the DHCA group was significantly higher than that in the SACP group at 120 min, 150 min, and 180 min of reperfusion ($p=0.0001$, 0.012, and 0.0001, respectively, Fig. 4a).

Cerebral microdialysis

During CA, the glucose levels of the DHCA group decreased significantly, but those of the SACP group remained relatively stable during the course of the experiment ($t=5.835$, $p=0.000$, Fig. 4b, 5a). The lactate levels in the SACP group were lower than those in the DHCA group, with significance at every time point

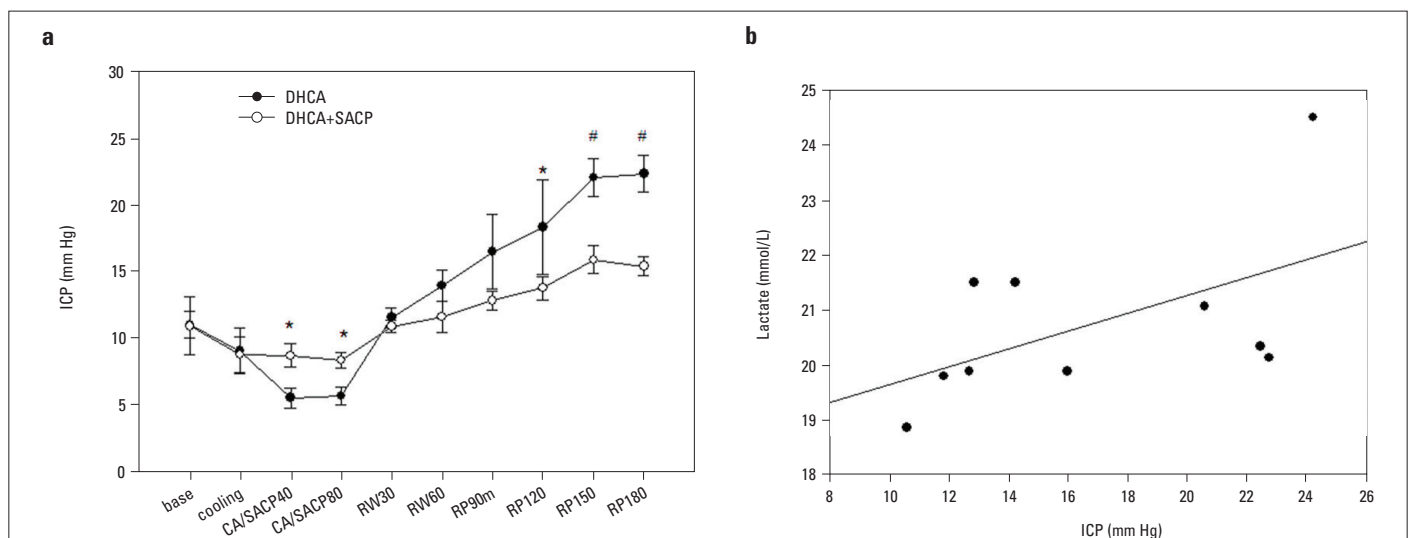


Figure 4. The dynamic change of intracranial pressure (ICP) (a) in both groups, and correlation analysis (b) between cerebral lactate and ICP during reperfusion in the DHCA group ($r=0.64$, $P=0.046$) are shown in the experiment, CA-circulatory arrest; RP-reperfusion, RW-rewarm; *, $P<0.05$; #, $P<0.01$

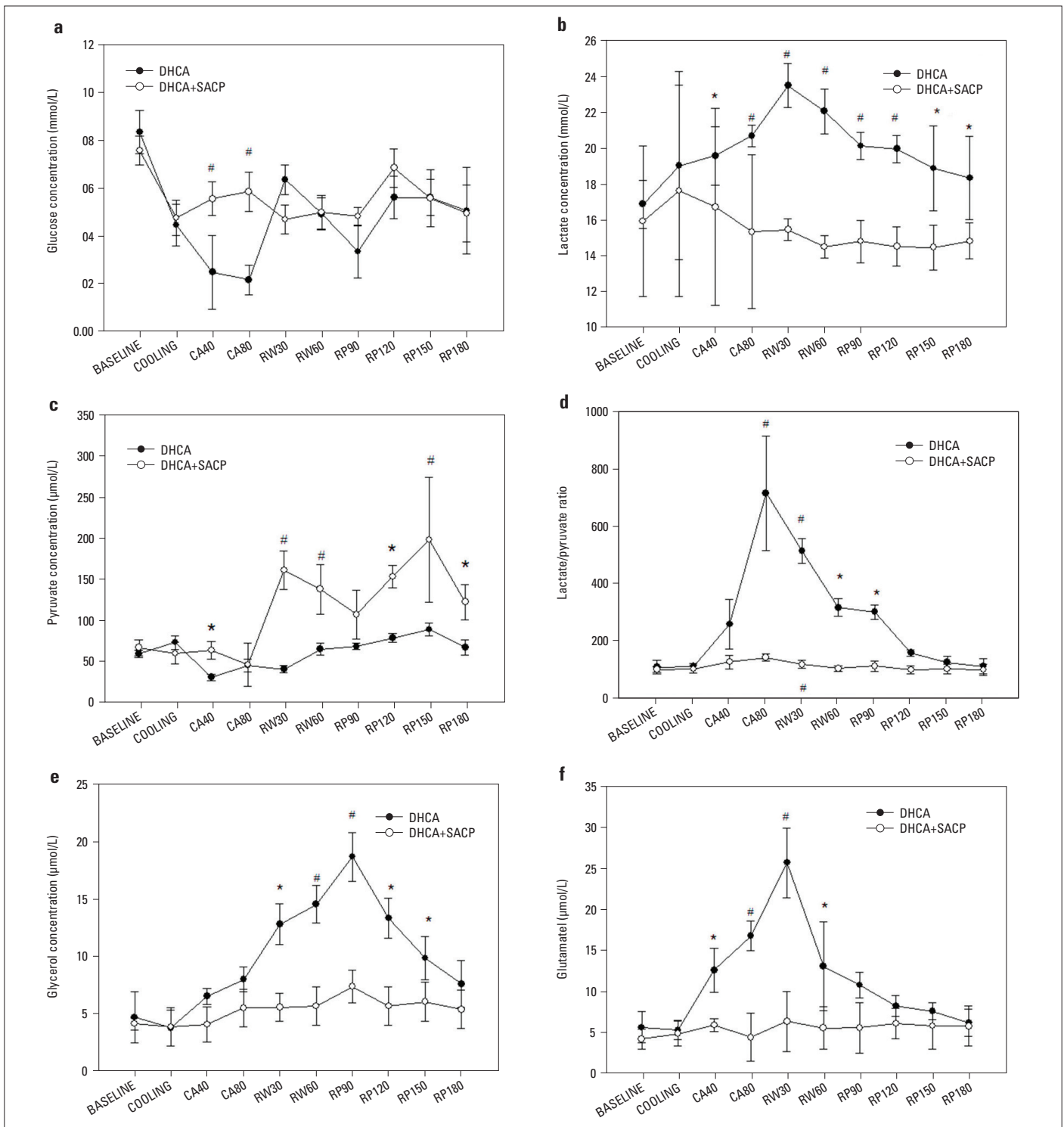


Figure 5. Cerebral cortex microdialysis results for the DHCA and SACP groups. (a) glucose; (b) lactate, (c) pyruvate; (d) lactate/pyruvate ratio; (e) glycerol; (f) glutamate. *, $P < 0.05$, #, $P < 0.01$. CA

CA - circulatory arrest; RP - reperfusion; RW - rewarm

after CA 40 min ($p < 0.05$, Fig. 5b). A positive correlation existed between the cerebral lactate and ICP during reperfusion in the DHCA group ($r = 0.64$, $p = 0.046$). The pyruvate levels in the DHCA group decreased markedly in the CA period, whereas those in the SACP group remained stable. Compared with a slow rise af-

ter 30 min of rewarming in the DHCA group, there was a sharp increase in the pyruvate value in the SACP group, which reached the peak at 150 min of reperfusion (Fig. 5c). The L/P ratio was constantly maintained at the baseline level in the SACP group. There was a rapid increase after cooling, with the peak observed at CA

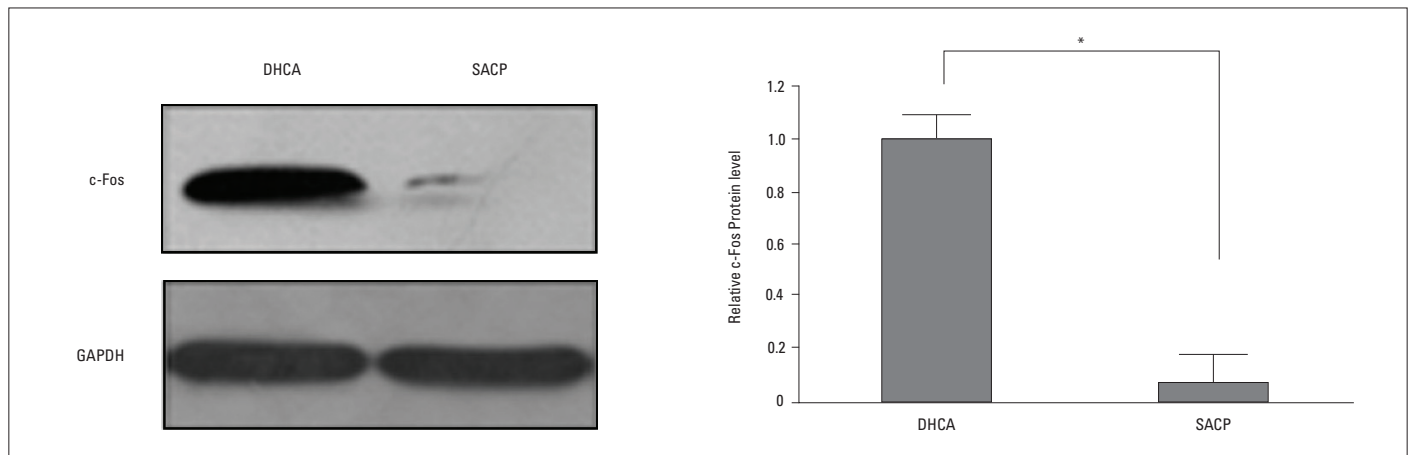


Figure 6. Western blotting for relative C-FOS protein levels. C-FOS of the SACP group was significantly lower than that of the DHCA group ($t=3.304$, $P=0.012$).

80 min in the DHCA group; however, the value finally returned to just slightly above the baseline level. There were significant differences from CA time points to 90 min of reperfusion ($p=0.0039$, Fig. 5d). The glycerol levels of the DHCA group reached the highest level after 90 min of reperfusion, followed by a persistent decrease to near the baseline level at RP 90 min. There was considerable significance found in the middle of the 5 time points compared with the SACP group ($p<0.05$, Fig. 5e). Contrary to the glutamate values of the SACP group, those of the DHCA group represented a vigorous fluctuation, which increased markedly parallel to the cooling ($p<0.05$), reaching the peak level after 30 min of rewarming ($p<0.01$); the value subsequently declined and slowly returned to the baseline level at RP 180 min (Fig. 5f).

Western blot

Expression levels of C-FOS were assayed using western blot analysis (Fig. 6). Levels of C-FOS protein in the SACP group were significantly lower than those in the DHCA group ($t=3.304$, $p=0.012$).

Discussion

The results of our study demonstrate that the brain is susceptible to cerebral injury during the rewarming period and that SACP can effectively decrease cerebral injury due to ischemia. The role of serum S100 in assessing brain damage secondary to ischemia and trauma has been questioned by many experts since 2000 (18, 19). However, this problem can be easily solved by detecting serial serum S100 levels along with other markers and by carefully monitoring peripheral injury (19), and thus the reliability of S100 as a predictor of secondary cerebral injury.

To assess the possibility of cerebral injury in both groups, C-FOS and fluorescence TUNEL were introduced. C-FOS is the most typical marker representing cerebral injury among members of the immediate early genes family, which play “the third messenger” role in transducing extracellular stimulation into an intracellular signaling cascade (20). These stimulations can in-

clude ischemia, injury, pain, and epilepsy. Apoptosis is one of the two major mechanisms of neuronal cell death and can be quantified based on the AI (21). The DHCA group had a higher C-FOS protein expression level with a higher AI compared with the SACP group, indicating that the DHCA group suffers more severe cerebral injury than the SACP group. SACP may further display neuroprotection by blocking apoptosis pathways.

Multiple neuromonitoring methods were strongly recommended to assess brain protection during DHCA, such as obtaining jugular venous bulb saturation ($SjvO_2$), near-infrared spectroscopy, electroencephalography (EEG), transcranial Doppler (TCD), and ICP level measurements. ICP is considered as a significant physiological indicator in traditional neuroscientific monitoring. In the recent study by Hagl et al.(22) ICP was established as an important predictor of cerebral injury after HCA, and a significant correlation between ICP levels and behavioral scores was revealed. Although the ICP levels of both groups increased to different extents after reperfusion, those of the SACP group were apparently lower than those of the DHCA group. A lower ICP level indicates milder brain edema and lower cerebral vascular resistance as well as better cerebral perfusion. A positive correlation was also found in the DHCA group between cerebral lactate and ICP levels during reperfusion, suggesting that appropriate de-ICP treatments improve local microenvironment metabolism during reperfusion.

Nevertheless, the abovementioned four methods fail to provide enough cerebral metabolism information (23). Microdialysis is the only method that can be used to detect real-time and in vivo metabolism change, which may have a pivotal vantage point in understanding the pathogenesis of neurological dysfunction (11). Normal brain function relies heavily on internal environment homeostasis, the function of which is equal to that of the extracellular neuronal microenvironment homeostasis. There are no glycogen reservations in neurons, which is a characteristic distinguishing them from skeletal muscles and hepatocytes. Literary references support the fact that glucose has a neuropro-

tective effect (24, 25), while others argue that hyperglycemia has a detrimental effect (26). In the present study, we observed that the cerebral glucose level in the SACP group remained relatively stable and had higher levels at every time point compared with that in the DHCA group. Meanwhile, a satisfactory outcome was achieved in the SACP group for other endpoint parameters, fluorescence TUNEL, and electron microscope, which detected mild damage resulting from histological changes and lower apoptosis indices, respectively. Consequently, these results support the premise that stable and acceptable cerebral glucose levels might have a neuroprotective effect. Our results were consistent with those of Pokela et al. (27) and Cavus et al. (28) who posited that glucose is a marker with the most important predictive factors in postoperative death and cerebral function recovery.

Generally speaking, glucose in the central nervous system serves as the main substrate of aerobic glycolysis; however, other pathways do work under conditions of oxygen and glucose deprivation. When glucose is anaerobically metabolized, astrocytes can produce lactate for the aerobic metabolism of neurons at hypoxia/anoxia (29). Another study claimed that the aerobic utilization of lactate instead of glucose fuels the recovery of synaptic function during reoxygenation (30). Lactate and pyruvate are the end products of anaerobic glycolysis and aerobic glycolysis, respectively. Therefore, the lactate/pyruvate ratio stands for the cytosolic ratio of the reduced/oxidized forms of nicotinamide adenine dinucleotide (NADH) and characterizes the relationship between aerobic and anaerobic metabolism, making it a reliable variable that indicates the state of cell energy metabolism (31). In this experiment, the constant increase of lactate and its further increase after declamping confirmed that the observed interstitial accumulation was due to CA in the DHCA group. In comparison with the DHCA group, the amount of cerebral lactate in the SACP group fluctuated around the baseline level because the continuous perfusion provided enough oxygen and substrate as well as the flushness effect. The most striking finding was that there was a positive linear correlation between lactate and ICP levels when reperfusion began. In other words, a higher ICP might result in worse ischemia during the reperfusion phase. The lactate/pyruvate ratio of the SACP group remained stable. In contrast, that of the DHCA group increased markedly after CA, reaching the peak at the end of this phase, which suggests that a longer duration leads to a more severe cerebral ischemia at extreme ischemia periods.

Glycerol is produced during the degradation of membrane phospholipids and serves as a sensitive and reliable marker of cerebral ischemia (32). Phospholipids have been shown to be major components of cell membranes as well as the cerebral tissue, which can regulate permeability and fluidity. In EROL's study, cerebral glycerol in piglets with a 90-min DHCA increased progressively and reached the peak by at least 45 min after reperfusion. Jorge et al. (33) also discovered the increasing glycerol level in piglets that underwent a 60-min DHCA. They observed that the peak appeared around 60 min after piglets were weaned

off CPB. The glycerol levels in the DHCA group increased, reaching the peak 90 min after reperfusion in our study. Nevertheless, the cerebral glycerol level of SACP remained stable.

Glutamate is also used as a parameter to evaluate cerebral injury with prompt increases glutamate release after the injury. High levels of cerebral glutamate, reaching the peak 30 min after rewarming, were discovered in animals that died as late as 6–8 h postoperatively at studied intervals throughout the experiment. Glutamate levels in the DHCA group were found to have been maintained at higher levels than those in the SACP group in our experiment, reaching the peak 30 min after rewarming.

In addition, we found that there were significant differences between the time points between two groups in most microdialysis variables except glycerol, demonstrating that SACP improved cerebral oxygen and energy metabolic results even with a shorter DHCA duration in less than 40 min. This conclusion gives a clear response to the heated debate (34) over which neuroprotection method should be utilized for about a 40-min-interval CA during clinical work. We recommend SACP as the first-choice cerebral perfusion approach both in shorter or prolonged DHCA.

Study limitations

There were, however, limitations to the present study. First and foremost, no postoperative data that were relevant to cerebral function recovery, such as a neurological behavioral score, which would be a more definitive measure supporting the neuroprotective effect of SACP, were collected. This study aimed to explore metabolism in cases with acute ischemia instead of chronic cases, and thus, postoperative variables were beyond our study design. Second, no CPB control group was established to discover differences in cerebral metabolism between routine extracorporeal circulation and SACP as systemic CA. Previous studies have mostly been conducted on DHCA and SACP groups, with which this study followed suit. Furthermore, the experimental data would be difficult to effectively coordinate and analyze with more than two groups. Nevertheless, these aspects will be taken into consideration in future studies.

Conclusions

The present study demonstrates that SACP has a neuroprotective effect that is superior to DHCA alone because SACP allows for milder damage under the electron microscope, lower C-FOS protein expression, AI, ICP, and serum S100, as well as better microdialysis energy metabolic parameters. Cerebral lactate is a reliable marker reflecting ICP during reperfusion using DHCA. This study confirms the validity of SACP as a superior neuroprotective strategy for both mild and particularly prolonged DHCA.

Acknowledgment: This work is supported by the Pearl River Scholar Program (No.80000-3210003), National Natural Science Foundation of China (No.81370215, No.81460290, No.81400307, and No.81560039), National Science Foundation of Jiangxi Province (No.20142BAB205041), Nat-

ural Science Foundation of Guangdong Province (No.2015A030313168), Educational Department Foundation of Jiangxi Province (No.GJJ14695), and Health and Planning Family Commission Funds of Jiangxi Province (No.20155427).

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – Z.T., M.L.; Design – G.C.; Supervision – J.R.; Fundings – J.Y., Z.T.; Materials – Z.C.; Data collection &/or processing – X.Y.; Analysis &/or interpretation – X.Y.; Literature search – Z.W.; Writing – Z.T., Z.W.; Critical review – Z.T., Z.W.

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