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Sodium Nitroprusside Enhanced CPR and intra-CPR Hypothermia

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Abstract

Objective : Therapeutic Hypothermia (TH) is thought to improve neurologically intact survival when applied after Return of Spontaneous Circulation (ROSC) is achieved in patients who suffer a cardiac arrest. Intra-CPR cooling may accelerate the time to reach TH and thus enhance its neurological benefit. Sodium Nitroprusside Enhanced Cardiopulmonary Resuscitation (SNPeCPR) has been shown to accelerate intra-CPR cooling compared to standard CPR. The aim of this study is to assess which method of therapeutic hypothermia is the most efficient in decreasing brain temperature during SNPeCPR.

Methods: This study included 24 intubated and anesthetized swine. After induction of Ventricular Fibrillation (VF), animals were randomized to one of the following groups: 500cc cold saline infusion (group A), 500cc cold saline infusion plus surface cooling with ice packs (group B), surface cooling only (group C) or control/no cooling method applied (group D). After 10 minutes of VF, CPR was initiated. One minute after the initiation of CPR, the randomized intervention was initiated and abdominal binding was applied. SNP (2 mg) was administered at minutes 1, 4 and 8. Animals were defibrillated at minute10.

Results: Within 4 minutes of CPR, animals that received intravenous cold saline (Group A and Group B) had decreased their brain temperature by 0.5 °C lower compared to the groups that had not (Group C and Group D). Group B presented a superior heat exchange rate from blood to skin compared to group A.

Conclusion : It was observed that cold saline infusion during SNPeCPR accelerates cooling of the brain. Ice packs work synergistically by optimizing heat transfer from the blood to the skin. Further studies will assess the potential neurologic benefit of the combination of SNPeCPR with intra-CPR infusion of cold saline.

Keywords: Cardiac Arrest; Cardiopulmonary Resuscitation; Therapeutic Hypothermia

Introduction

Out-of-hospital cardiac arrest is a major cause of morbidity and mortality in the US, with nearly 395,000 people suffering from it annually. An estimated 85-90% of these patients die or develop severe neurologic dysfunction attributed to cardiac arrest [1,2]. Mild Therapeutic Hypothermia (TH) applied as soon as possible upon return of spontaneous circulation has been proposed as a means to achieve higher survival rates and better neurologic function in comatose patients who suffer an out-of-hospital cardiac arrest [3-5]. In animal models of cardiac arrest, TH increased survival and neurologic outcomes when applied during Cardiopulmonary Resuscitation (CPR) [6,7]. Delaying induction of TH for 15 minutes, after the initiation of CPR, diminishes the beneficial neurologic effects [8]. A cold saline infusion (of up to 2L) has been demonstrated as a safe way to decrease core temperature as compared to the conventional methods of surface cooling both in the hospital and pre-hospital, albeit with no definitive clinical beneficial results to date [9-12].

Sodium Nitroprusside Enhanced CPR (SNPeCPR) is a method of resuscitation that combines Active Compression-Decompression (ACD) with an Impedance Threshold Device (ITD), intravenous sodium nitroprusside administration and abdominal binding. ACD + ITD CPR have been shown to increase

short and long-term survival with favorable neurological function after out-of-hospital cardiac arrest in patients [13,14]. In a porcine model of cardiac arrest, SNPeCPR has been shown to increase brain and heart perfusion during CPR [15,16]. It has been observed that it increases return to spontaneous circulation rates [15,16]and also achieve improved cardiac function [16,17], 24-hour survival and neurologic function in animal models of cardiac arrest both in ventricular fibrillation and pulseless electrical activity [15,17,18]. In a previous study we did, it was demonstrated that SNPeCPR facilitates intra-CPR therapeutic hypothermia. This effect was abolished in the study groups that did not receive SNP or received both SNP and epinephrine [19].

In the present study, it was assessed which method of therapeutic hypothermia is the most efficient in decreasing brain temperature during SNPeCPR. It was hypothesized that a combination of intravascular and surface heat exchange is necessary for swift intra-CPR cerebral hypothermia induction. Our well-established porcine model of prolonged untreated VF and CPR was used [15,17-19].

Materials and Methods

All studies were conducted in female pigs (Yorkshire) weighing 40.7±2.09 Kg. Animal care was in accordance with the Guidelines for the Care and Use of Laboratory Animals. The Institutional Animal Care Committee of the Minneapolis Medical Research Foundation approved ofthe protocol.

Preparatory Phase

We are going to briefly describe the anesthesia, surgical preparation, data monitoring, and recording procedures used in this study as they have already been described previously indetail [20]. Animals were sedated by intramuscular use of ketamine (7 mL of 100 mg/mL, Ketaset, Fort Dodge Animal Health, Fort Dodge, Iowa) and then anesthetized with 0.8 - 1.2 % inhaled isoflurane till Ventricular Fibrillation (VF) induction.Anesthesia was resumed after return of spontaneous circulation (ROSC). Animals were intubated with size 7.0 endotracheal tubes and ventilated with a volume-control ventilator (Narcomed, Telford, Pennsylvania). Tidal volume (10 mL/kg) and respiratory rate were adjusted to maintain a target $PaCO_2$ of 35-45 mmHg and a target PO_2 of more than 80 as measured by arterial blood (Gem 3000, Instrumentation Laboratory, Lexington, Massachusetts).Pigs were kept at 37±0.2˚C blood temperature by use of a cutaneous warming/cooling device (Arctic Sun, Medivance Inc., Louisville, CO). Blood, skin, esophageal and brain temperatures were measured by using temperature probes inserted respectively in the descending aorta through the right femoral artery, subcutaneous tissue of the leg, upper esophagus, parietal lobe of the brain. Aortic blood pressure and right atrial pressure were continuously monitored by micromanometer-tipped (Mikro-Tip Transducer, Millar Instruments, Houston, Texas) catheters placed at the descending aorta and right atrium via the left femoral artery and right external jugular vein respectively. Intracranial Pressure (ICP) was measured by use of a Millar catheter inserted in the parietal lobe, after cannulating the skull with a drill. Carotid blood flow was measured using a surgically placed ultrasound probe (Transonic 420 series multichannel, Transonic Systems, Ithaca, New York) on the left internal carotid artery. Surface leads were used to record electrocardiography tracings. A respiratory monitor (CO_2SMO Plus, Novametrix Medical Systems, Wallingford, Connecticut) was measuring end tidal CO_2 ($ETCO_{2)}$, respiratory rate, tidal volume and oxygen saturation. A digital recording system (BIOPAC MP 150, BIOPAC Systems, Inc., CA, USA) was used to record and save all data.

Measurements and Recording

Intra-Thoracic Pressure (ITP), Aortic (Ao) pressure, Right Atrial (RA) pressure, intracranial pressure (ICP) and Carotid Blood Flow (CBF) (mL/min) were continuously recorded. Coronary Perfusion Pressure (CPP) during CPR was calculated by the numerical difference between aortic pressure and RA pressure during the decompression phase of CPR. Cerebral Perfusion Pressure (CePP) was calculated by the numerical difference between aortic pressure and ICP.

Experimental Protocol

After completion of the surgical preparation, and after the animal has had oxygen saturation of more than 94% and an $ETCO_2$of 35-42 for more than 5 minutes, VF was induced by use of a temporary pacemaker (St. Jude Medical, Minnetonka, Minnesota) inserted in the right ventricle. The ventilator was then disconnected from the endotracheal tube. During CPR, active compressions/decompressions were delivered using an automated device (Pneumatic Compression Controller, Ambu International, Glostrup, Denmark) as previously described [21]. Rate of compressions was 100/minute and the depth of compressions was ¼ of the anterior-posterior diameter of the pig. An Impedance Threshold Device (ITD) (-7mmHg ResQPOD TM, Advanced Circulatory Systems, Inc, Roseville, Minnesota) was used in all experiments. Asynchronous positive pressure breaths were delivered every 6 seconds using an Ambu bag. Abdominal binding was performed by manual application of pressure (≈90 mmHg) to the lower abdomen of the pig as previously described [15,18].

Protocol

Following 10 minutes of untreated VF, 24 pigs were treated for 10 minutes with SNPeCPR and they were randomized to receive one of the following: 1) infusion of 500 cc cold saline (group A), 2) infusion of 500 cc cold saline and surface cooling with ice packs (group B), 3) surface cooling alone (group C) or 4) nothing (control

group or group D). All cooling methods started at minute 1 of CPR. Cold saline was at a 4°C temperature and was administered via a peripheral vein at a maximum infusion rate (approximately 160mL/min). Sodium nitroprusside (2 mg) was administered via the external jugular vein at minutes 1, 4 and 8 of CPR. Abdominal binding was applied at minute 1 of CPR. At minute 10, the first defibrillation was attempted with 275 J (Lifepak 15, Physio-Control, Redmond, WA). If the animal did not have a Return of Spontaneous Circulation (ROSC) after three defibrillation attempts, 0.5 mg of epinephrine and 25 mg of amiodarone were given IV. If ROSC was unsuccessful, one defibrillation was delivered every 2 minutes and 0.5 mg of epinephrine was given every 4 minutes. At 15 minutes after initiation of CPR if ROSC was not achieved, all resuscitation efforts were stopped.

Post-ROSC Care

After ROSC was achieved, ventilation was resumed through the ventilator with room air and 0.6-1% isoflurane. Oxygen was administered at a rate of 4L/min if arterial O_2 saturation was below 90% aiming for an O_2 saturation of 90-94%. Epinephrine boluses of 0.1 mg (IV) were given every 5 minutes if mean arterial pressure was falling below 50 mmHg and the rhythm was stable. Sodium bicarbonate (50-100 mEq) was given as an IV bolus if pH was below 7.2.An external surface-cooling device (Arctic Sun, Medivance, Louiseville, CO) was applied right after ROSC set at maximum cooling rate. After a brain temperature of 34°C was reached, it was kept stable for a two-hour period after which the animals were euthanized.

Heat Exchange Rate estimation

Because at the initiation of CPR, every animal has an existing temperature difference (baseline ΔT) between blood and skin, it was decided to normalize the difference of Temperature between blood and skin at each minute of CPR by using the following formula: Normalized Temperature Difference Between Blood and Skin = (ΔT at each min-ΔT at baseline). With this formula,smaller differences represent higher heat exchange rates with the direction being core to skin and to the environment.

Heat exchange rate estimation was based on the following:

Assuming one-dimension steady state conduction, it is known (Fourier's law of thermal conduction) that:

$$Q = qA = -k\frac{dT}{dx}A = -\frac{k}{L}(Ti - To) \quad \text{A}$$

where Q is the heat flux, q is the local heat flux density, k is the material's conductivity (skin), L is the depth of the skin, Ti the temperature of the blood compartment, To the temperature of the surface of the skin compartment and the area of heat exchange. Assuming that the depth is constant and the temperature of the blood is the same in both groups that receive cold saline, it is concluded that the higher the area of heat exchange (A) and the lower the temperature of the skin is (To), the higher the heat exchange from the blood to the skin will be.

Echocardiographic Assessment of the Left Ventricle

Baseline and 2 hours post ROSC echocardiographic measurements of the left ventricle were taken with a transthoracic echocardiogram (Philips Sonos 5500 Ultrasound, Amsterndam, Netherlands, with an Agilent Technology S3 probe, Santa Clara, CA) as previously described [19].

Statistical Analysis

All results are presented as means±standard deviation. Comparisons between continuous variables in our groups were done using analysis of variance and t-test. Chi-square was used to determine statistical significance between proportions. A p value of 0.05 was used as a cut-off to determine significance.

Results

Return of spontaneous circulation rates between treatment groups were not statistically significant different (1/6, 5/6, 3/6 and 2/6 animals in groups A, B, C and D respectively). Additionally, the number of shocks needed to establish ROSC was not statistically different between treatment groups (2, 2.6±1.52, 1.33±0.58 and ±0 in groups A, B, C and D respectively; p=0.24). When groups were compared in the amount of epinephrine and amiodarone needed to achieve ROSC, no statistically significant difference was found (epinephrine dose in mg: 0.7, 0.42±0.24, 1±0.5 and 0.5±0; amiodarone dose in mg; 25, 30±11.18, 25±0, 25±0 in groups A, B, C and D, respectively, p= 0.10 and p=0.66)

Temperatures During CPR

For each treatment group, the change in brain temperature (ΔT) during CPR was calculated as the difference between the temperature at the initiation of CPR and each minute during CPR thereafter (Figure1). The groups that received cold saline infusion (Groups A and B) significantly augmented heat exchange in the brain compared to the other groups as it can be seen by the progressive decrease of brain temperature compared to baseline within four minutes of CPR. (Figure1, Table 1). Furthermore, within 8-10 minutes of CPR, animals that received intravenous cold saline had decreased the brain temperature by 1°C lower compared to the controls (Figure 1, Table 1). Figure2 depicts the temperatures of the brain, esophagus, blood and skin during CPR Table 2.

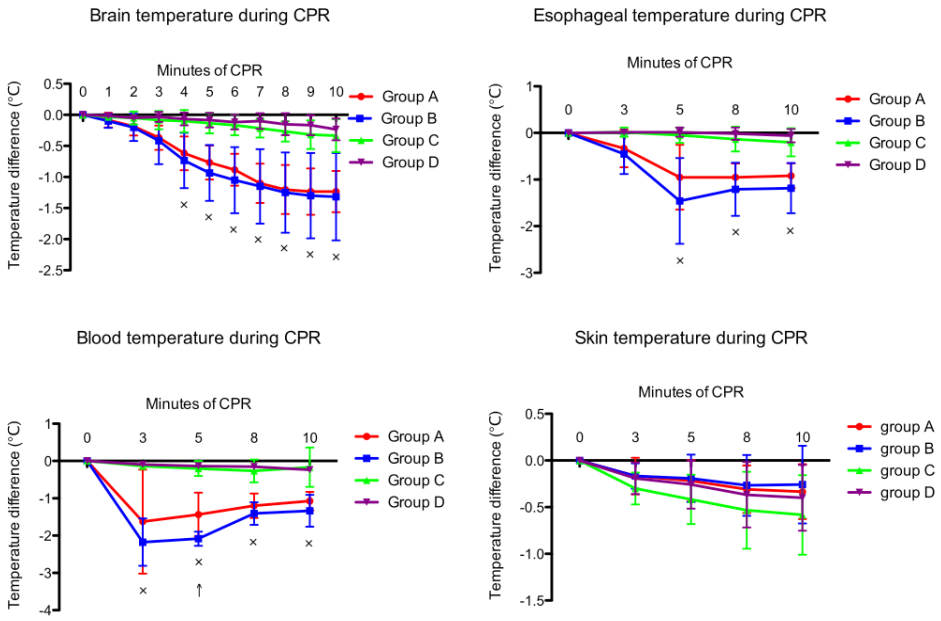

Figure 1: Normalized temperatures in the brain, esophagus, blood and skin during CPR. Temperatures are in Celsius degrees (°C). Group A received 500cc cold saline, Group B received 500 cc cold saline plus surface cooling with ice packs, Group C received only surface cooling, Group D is a control group. x indicates statistically significant difference between groups that received cold saline (groups A and B) and groups that did not (groups C +D); $p<0.05$. ↑ indicates statistically significant difference between group A and groups B; $p<0.05$.

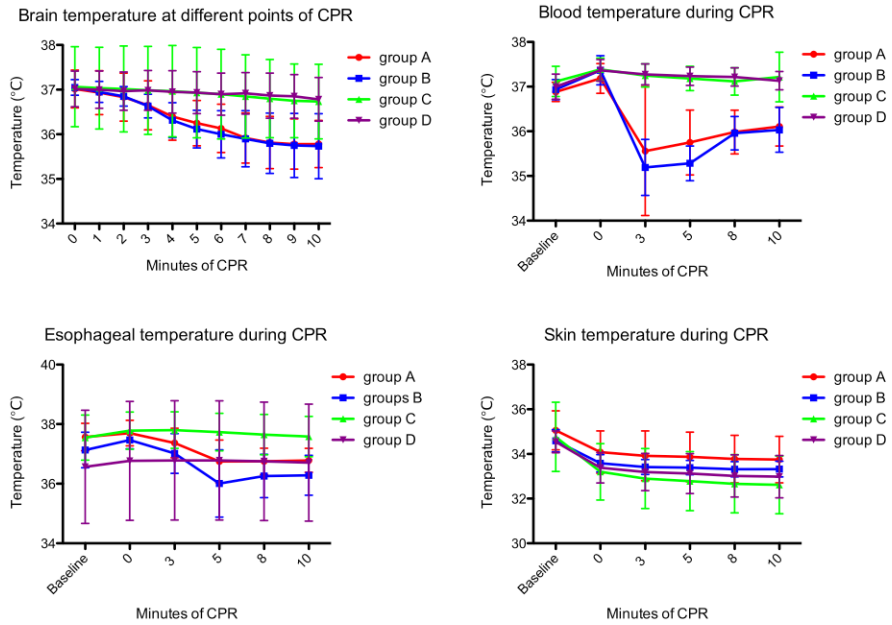

Figure 2: Absolute temperatures in the brain, esophagus, blood and skin at baseline and during CPR. Temperatures are in Celsius degrees (°C). Group A received 500cc cold saline, Group B received 500 cc cold saline plus surface cooling with ice packs, Group C received only surface cooling, Group D is a control group. x indicates statistically significant difference between groups that received cold saline (groups A and B) and groups that did not (groups C +D); $p<0.05$. ↑ indicates statistically significant difference between group A and groups B; $p<0.05$.

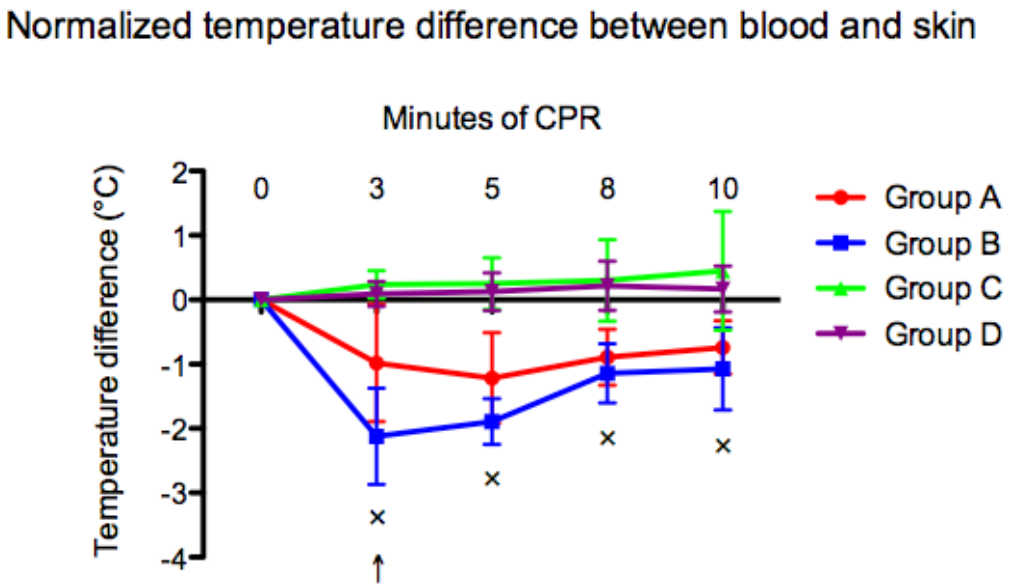

Figure 3: Normalized temperature difference between blood and skin during CPR. There is a statistically significant difference at the 3rd minute of CPR in temperature difference between groups A and B. In groups A and B, the temperature difference between blood and skin at the initiation of CPR gets smaller over time suggesting more efficient heat exchange. Group B seems to offer even greater heat exchange rate compared to Group A. Temperatures are in Celsius degrees (°C). Group A received 500cc cold saline, Group B received 500 cc cold saline plus surface cooling with ice packs, Group C received only surface cooling, Group D: control group. x indicates statistically significant difference between groups that received cold saline (groups A and B) and groups that did not (groups C +D); $p<0.05$. ↑ indicates statistically significant difference between group A and groups B; $p<0.05$.

Comparison groups	dT (4th minute of CPR)	P <	dT (10th minute of CPR)	P <
A-C	-0.516	0.05	-0.9	0.01
A-D	-0.55	0.05	-1.0	0.01
B-C	-0.63	0.001	-0.98	0.001
B-D	-0.66	0.001	-1.08	0.001
Difference in temperature (dT) is in Celsius degrees (°C). Group A received 500cc cold saline, Group B received 500 cc cold saline plus surface cooling with ice packs, Group C received only surface cooling, Group D is a control group.				

Table 1: Comparison of brain temperature differences between groups 4 and 10 intra-CPR.

Temperature difference between blood and skin was significantly different when comparing Groups A+B with Groups C+D from the 3rd minute of CPR (Figure 3).

	Groups			
Parameter	Group A	Group B	Group C	Group D
SBP	75.4±13.4	83.2±9.8	77±7.2	89.3±12
DBP	62.8±10.8	70.3±10.2	64.1±7.4	75.4±10.3
RA	3.1±2.3	6.1±1.5	5.4±2.4	5.5±3.4
CBF	332±153	415±92	304±183	467±47
ICP	24.8±3.4	21.7±3.8	21.3±7.9	26.2±2.5
CPP	59.8±11	65.4±9	58.7±7.8	68.8±8.4
CePP	50.5±11	61.4±12.2	53.2±6.9	63.7±13
EtC02	39.2±1.7	40.5±3	39±1.3	40.7±1.2

Values are shown as mean±sem. Pressures are presented in mm Hg and flow in mL/min. Group A received 500cc cold saline, Group B received 500 cc cold saline plus surface cooling with ice packs, Group C received only surface cooling, Group D is a control group, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, RA: Right Atrial Pressure, CBF: Cerebral Blood Flow, ICP: Intracranial Pressure, CPP: Coronary Perfusion Pressure, CePP: Cerebral Perfusion Pressure, EtC02: End Tidal Carbon Dioxide.

Table 2: Hemodynamic parameters of the groups at baseline.

		Groups			
Parameter	Min	Group A	Group B	Group C	Group D
SBP	5	46.9±5.5	59.6±16.5	42.6±11.9	41.7±4.2
	10	39.6±4.2	54.1±23.8	40.5±10.4	37.2±4.7
DBP	5	22.6±6.3	28.9±6.2	22.1±4.7	22.4±4
	10	21.5±5.8	21.7±7.8	17.7±12.1	18.7±3.3
RA	5	15.9±7.9	13.5±3.8	8.7±3.9	10.5±3.2
	10	12±4	12.1±4	8.2±3.5	6.6±2.8
CBF	5	194±100	349±129	218±109	293±59
	10	197±105	309±100	198±128	281±59
ICP	5	41.5±4.6	35.1±11.8	30.4±3.9	35.2±7.9
	10	38.6±6.9	33.5±9.8	28±12.4	32.3±10
CPP	5	6.7±9.9	15.4±8.9	13.5± 5.4	11.6±3.5
	10	9.5±6.4	9.7±11.2	9.5±9.8	10.7±2.4
CePP	5	-3.1±10.1	18.7±9.7	4±6.6	2.6±13.1
	10	-6.2±9.6	16.5±18.2	2.7±9	2.2±16.4
EtCO2	5	34.5±4.7	34.8±3.1	29.2±9.8	35.1±5.7
	10	35±7	35.4±7.2	24.3±10.8	33.8±5.7

Values are shown as mean±sem. Pressures are presented in mm Hg and flow in mL/min. Group A received 500cc cold saline, Group B received 500 cc cold saline plus surface cooling with ice packs, Group C received only surface cooling, Group D is a control group, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, RA: Right Atrial Pressure, CBF: Cerebral Blood Flow, ICP: Intracranial Pressure, CPP: Coronary Perfusion Pressure, CePP: Cerebral Perfusion Pressure, EtC02: End Tidal Carbon Dioxide.

Table 3: Hemodynamic parameters of the groups during cardiopulmonary resuscitation.

Hemodynamics

There was no difference in hemodynamics between the groups at baseline. At the 5th minute of CPR, Group B had higher systolic pressures as compared to Group C and Group D (59.60±16.49 mmHg versus 42.64±11.91 mmHg, 41.67±4.17 mmHg respectively, $p<0.05$). At the 5th minute of CPR, Group B had higher cerebral perfusion pressure than Group A, C and D (18.66±9.68 versus -3.13±10.14, 4.07±6.55 and 2.55±13.13 respectively; $p<0.05$).

Arterial Blood Gases

Baseline arterial blood gas characteristics were no different at baseline. There was no statistically significant difference between groups A, B, C and D at 15, 60 and 120 minutes' post ROSC in the following blood gas parameters: pH, pO_2, pCO_2, bicarbonate level and base excess.

Echocardiography Measurements

Transthoracic echocardiography was performed (Philips Sonos 5500 Ultrasound, Amsterdam, Netherlands) in all animals at baseline and 2 hours post-ROSC. Assessment of the left ventricle showed no difference in ejection fractions between groups at baseline (group A: 58.3±8%, group B: 55±6, group C: 58±5, group D: 54±14) and 2 hours post-ROSC (group A: 50%, group B: 41±7, group C: 53±13, group D: 40±7). A cardiologist blinded to treatments evaluated the ejection fractions using Simpson's method of volumetric analysis. All inotropic medicine was stopped at least 15 minutes before assessment of the left ventricle.

Cardiac Biomarkers

Serum samples, for troponin I and CK-MB measurements, were obtained at baseline and 2 hours post ROSC. Troponin I levels in the 500 cc + surface cooling group were lower than in the surface cooling alone group 2 hours post ROSC (4.45±3.46 µg/L, 12.05±2.57 µg/L respectively; $p=0.037$). There was no statistically significant difference at baseline between groups neither for troponin levels nor for CK-MB levels (Figure 4).

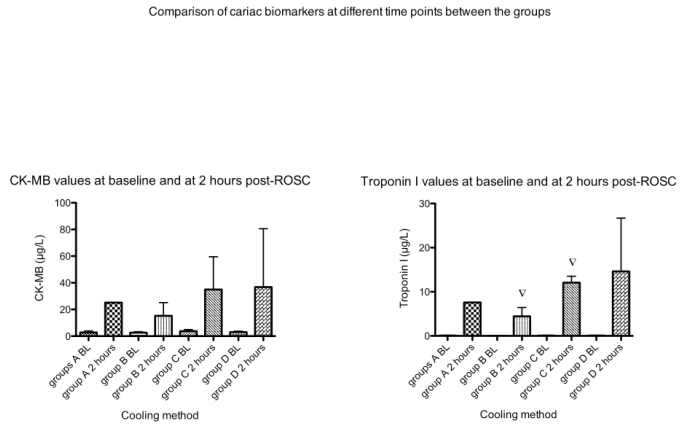

Figure 4: Comparison of cardiac biomarkers at baseline and 2 hours post-ROSC between treatment groups. There was no difference between Troponin I (µg/L) and CK-MB (µg/L) values at baseline. There was a statistically significant difference in Troponin I values between Group B and Group C 2 hours post ROSC. Group A received 500cc cold saline, Group B received 500 cc cold saline plus surface cooling with ice packs, Group C received only surface cooling, Group D is a control group. v indicates statistically significant difference between group B and groups C; $p<0.05$.

Discussion

In the present study, it was found that a combination of surface cooling and intravascular cold saline infusion during CPR can significant augment heat exchange rate and can lead to a significant decrease in brain temperature within 4 minutes of CPR. Our study shows that infusion of cold saline is much more effective than surface cooling methods alone in lowering core temperature in the setting of SNPeCPR. Despite peripheral vasodilation during SNPeCPR, surface cooling alone is not as effective in lowering blood and brain temperature.

It has been shown that an infusion of 2 L of cold saline is safe post cardiac arrest, with the same incidence of pulmonary edema as without infusion [10,11]. We chose to infuse to infuse

500ml of cold saline in the animals as swine have lower weight than human (40.7±2.09 Kg vs 72 Kg of an average person), and thus a lower blood volume. We hypothesize that we could have infused a higher volume of saline and achieve a higher temperature drop safely. We infused cold saline through a peripheral vein, as it would simulate a more feasible route of administration in the clinical field than that of a central vein. We do not know if the same effects we observed with intravenous infusion of cold saline could be seen with intraosseous administration. We have not investigated the long term outcomes cold saline infusion has.

In previous studies, it has been shown that the difference of brain to blood temperature is narrower and brain flow is higher when ACD-ITD is applied during CPR [22]. SNPeCPR increases blood flow further so that tissues can be cooled rapidly and also vasodilates to enhance heat exchange [19]. Therefore, the combination of SNP and cold saline infusion seems to be superior.

In our previous study, it was observed that SNPeCPR improved heat exchange through vasodilation of the vessels of the skin lowering the ΔT between blood and skin ($\Delta T_{blood\text{-}skin}$) when compared to SNPeCPR plus epinephrine administration and standard CPR [19]. In groups A+B, a significant decrease over time of the temperature difference between blood and skin that was present at the initiation of CPR was observed, compared to groups C+D suggesting that there is a more efficient heat exchange rate with the use of intravenous cold saline. Finally, group B presented a superior heat exchange rate compared to group A as it can be seen in Figure3.

There seems to be a benefit in applying surface cooling with ice packs with cold saline administration as the difference between blood and skin temperature is more rapidly decreased. This means a higher heat exchange in this group, which is explained by the higher difference between blood and skin when ice packs are applied on the skin and the vasodilation that SNP offers.

Limitations

This is a porcine model and the heat exchange rates and skin characteristics may not reflect human parameters. As such, physiologic observations in humans are warranted. Our results do not provide evidence of clinical benefit but suggest mild cardio protection as seen by the lower troponins with the group that received intravenous and external cooling. Survival studies are on the way in our laboratory to put the current results in clinical perspective.

Conclusion

In conclusion, it was observed that cold saline infusion during SNPeCPR accelerates cooling of the brain. Ice packs work synergistically by optimizing heat transfer from the blood to the skin. To conclude that this cooling method can be regarded as a survival benefit requires further investigation.

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