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Sodium Nitroprusside Enhanced Cardiopulmonary Resuscitation Improves Short Term Survival in a Porcine Model of Ischemic Refractory Ventricular Fibrillation

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Abstract

Introduction—Sodium nitroprusside (SNP) enhanced CPR (SNPeCPR) demonstrates increased vital organ blood flow and survival in multiple porcine models. We developed a new, coronary occlusion/ischemia model of prolonged resuscitation, mimicking the majority of out-of-hospital cardiac arrests presenting with shockable rhythms.

Hypothesis—SNPeCPR will increase short term (4-hour) survival compared to standard 2015 Advanced Cardiac Life Support (ACLS) guidelines in an ischemic refractory ventricular fibrillation (VF), prolonged CPR model.

Methods—Sixteen anesthetized pigs had the ostial left anterior descending artery occluded leading to ischemic VF arrest. VF was untreated for 5 minutes. Basic life support was performed for 10 minutes. At minute 10 (EMS arrival), animals received either SNPeCPR (n=8) or standard ACLS (n=8). Defibrillation (200J) occurred every 3 minutes. CPR continued for a total of 45 minutes, then the balloon was deflated simulating revascularization. CPR continued until return of spontaneous circulation (ROSC) or a total of 60 minutes, if unsuccessful. SNPeCPR animals received 2 mg of SNP at minute 10 followed by 1 mg every 5 minutes until ROSC. Standard

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All studies were performed with approval from the Institutional Animal Care Committee of the University of Minnesota (protocol 1508-32926A).

CONFLICT OF INTEREST

None of the authors have any financial or personal relationships with people or organizations that could have inappropriately influenced this work.

ACLS animals received 0.5 mg epinephrine every 5 minutes until ROSC. Primary endpoints were ROSC and 4-hour survival.

Results—All SNPeCPR animals (8/8) achieved sustained ROSC versus 2/8 standard ACLS animals within one hour of resuscitation ($p=0.04$). The 4-hour survival was significantly improved with SNPeCPR compared to standard ACLS, 7/8 versus 1/8 respectively, $p=0.0019$.

Conclusion—SNPeCPR significantly improved ROSC and 4-hour survival compared with standard ACLS CPR in a porcine model of prolonged ischemic, refractory VF cardiac arrest.

Keywords

sodium nitroprusside enhanced CPR; ventricular fibrillation; cardiac arrest; ischemic refractory ventricular fibrillation; advanced cardiopulmonary life support; cardiopulmonary resuscitation; ST elevation myocardial infarction; haemodynamics

INTRODUCTION

Current resuscitation interventions for the approximate 380,000 patients who suffer out-of-hospital cardiac arrest (OHCA) each year in the United States results in an average functionally favorable survival rate ranging from 6–15%.¹ Most do not survive or get admitted to the hospital, and most are pronounced dead in the field. However, 25–30% of patients present with the shockable rhythms of ventricular fibrillation and/or tachycardia (VF/VT)^{2–5} and experience survival rates ranging from 30–50%.^{1–3} Thus, the VF/VT population represents the overwhelming proportion (up to 85%) of OHCA survivors.⁶

Irrespective of the presence or absence of ST elevation on the post-resuscitation 12-lead electrocardiogram (ECG), the VF/VT OHCA population has been shown to have a high prevalence (~ 60%) of acute coronary occlusion and/or coronary artery ischemia.^{7–12} This prevalence is even higher for the 50–70% of patients with refractory VF/VT.^{7–12} Recognizing this underlying, potentially reversible cause for refractory VF/VT, the Minnesota Resuscitation Consortium established the first organized refractory VF/VT protocol in the nation. The protocol includes optimizing OHCA CPR hemodynamics using mechanical CPR devices, facilitating early emergency medical services (EMS) transport to the cardiac catheterization laboratory (CCL), delivering emergent percutaneous coronary intervention (PCI), and providing effective hemodynamic support using intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) before and/or after PCI procedures. Preliminary experience with this approach demonstrates a functionally favorable survival rate of 50%, despite prolonged CPR and resuscitation efforts.⁷

Sodium Nitroprusside enhanced CPR (SNPeCPR) has been shown to improve CPR generated blood flow to the heart and brain,^{13–17} improve cardiac function after pulseless electrical activity (PEA) and VF arrest, and cerebral recovery in prolonged CPR and prolonged untreated VF porcine models of cardiac arrest.^{14,15,18}

We hypothesized that during prolonged resuscitation for ischemic refractory VF, the use of SNPeCPR advanced cardiac life support (ACLS) would lead to a higher return of spontaneous circulation (ROSC) rate and survival. To test this hypothesis, we developed a

porcine model of severe refractory ischemic VF with ostial left anterior descending (LAD) balloon occlusion and CPR. In this model, return of spontaneous circulation (ROSC) in animals treated with standard ACLS is rare during coronary occlusion, simulating very closely the clinical presentation of patients treated in the CCL by the Minnesota Resuscitation Consortium refractory VF/VT protocol.⁷

METHODS

This study was approved by the Institutional Animal Care and Use Committee of the University of Minnesota. All animal care was compliant with the National Research Council's 1996 Guidelines for the Care and Use of Laboratory Animals (protocol number: 12-11). All studies were performed by a qualified, experienced research team in Yorkshire female farm bred pigs (40±2Kg). A certified and licensed veterinarian assured the protocols were performed in accordance with the National Research Council's Guidelines.

Preparatory Phase

The aseptic surgical preparation, anesthesia, data monitoring and recording procedures used in this study are part of our approved protocols. Animals were fasted overnight. Intramuscular ketamine (10 mL of 100 mg mL⁻¹) was used for sedation followed by inhaled isoflurane (0.8–1.2%). Pigs were intubated with a size 7.0 endotracheal tube then ventilated with room air, using an anesthesia machine (Narkomed, Telford, Pennsylvania), with a tidal volume of 10 ml kg⁻¹ and a respiratory rate adjusted to continually maintain a PaCO₂ of 40 mmHg and PaO₂ of at least 80 mmHg (blood oxygen saturation > 95%). Normothermia was maintained with a warming blanket (Bair Hugger, Augustine Medical, Eden Prairie, Minnesota). Post resuscitation therapeutic hypothermia (34°C) was achieved by the use of Blanketrol cooling blanket (Cincinnati Sub Zero). Central aortic blood pressure was recorded continuously with a Millar catheter (Mikro-Tip Transducer, Millar Instruments, Houston, TX, USA) placed in the descending thoracic aorta. A second Millar catheter was inserted in the right atrium via the right external jugular vein. Animals received an intravenous heparin bolus (100 units/kg).

Heparin is necessary to avoid intracoronary and intra-aortic thrombosis due to the presence of coronary guide catheters, coronary dilation balloons and wires. Arterial blood gases (Gem 3000, Instrumentation Laboratory) were obtained at baseline, and then every 5 minutes until 45 minutes, and then every hour starting at 1 hour until death or sacrifice at 4 hours. Electrocardiograms were continuously recorded. Hemodynamic data were continuously monitored and recorded (LabVIEW, National Instruments). Coronary perfusion pressure (CPP) was calculated as the difference between diastolic blood pressure and right atrial pressure. End tidal carbon dioxide (ETCO₂), tidal volume, minute ventilation, and blood oxygen saturation were continuously measured (COSMO Plus, Novamatrix Medical Systems, Wallingford, Connecticut).

Experimental Protocol

After the animals were prepared in the manner described above, percutaneous femoral arterial sheaths were placed. The left coronary artery was engaged using an AL 0.75 short

tip guide catheter. A coronary guide wire was placed in the distal LAD and a 4.0×16 mm balloon was inflated in the ostial portion of the LAD before the first diagonal. The majority of the animals (13/16) developed ventricular fibrillation spontaneously. If the animal did not arrest spontaneously within 5 minutes, VF was induced via electrical stimulation in the right ventricle (via the right external jugular vein access). Ventricular fibrillation was left untreated for 5 minutes to simulate the average arrival time of first responders in our state of Minnesota. At 5 minutes of VF, basic life support (BLS) was initiated with chest compressions, using an automated system in which we determine the precise depth of compression and decompression. The compression decompression duty cycle was 50%, the rate was 100/min and the target depth was 20% of the antero-posterior thoracic diameter at the mid sternal level. All animals received automated active compression decompression (ACD) + impedance threshold device (ITD) CPR regardless of group assignment.² At that point, animals were randomized based on a computer-generated list, to be treated with either SNPeCPR or standard ACLS CPR at minute 10 of CPR (to simulate ACLS initiation with paramedics arriving at the scene). In the SNPeCPR group, at minute 10 of CPR, the animals were given 2 mg IV sodium nitroprusside followed by 1 mg every 5 minutes. They did not receive epinephrine. Animals treated with standard ACLS CPR received 0.5 mg of epinephrine every 5 minutes starting at minute 10 of CPR as well to simulate the equivalent adult human dose/weight. Defibrillation with 200J biphasic shocks were delivered every 3 minutes. ROSC was defined as an organized cardiac rhythm with a mean arterial pressure of at least 50 mmHg for at least 30 seconds. Figure 1 shows the protocol timeline and Figure 2 shows the coronary occlusion model.

In all animals, the balloon was deflated 45 minutes after initiation of CPR. If the animal did not achieve ROSC after another 15 minutes of CPR, the animal was declared dead at minute 60 of CPR. Animals were monitored and survived until 4 hours.

Infarction size determination

Before sacrifice, the right and left coronary arteries were simultaneously engaged. An over-the-wire 4.0×16 mm balloon was placed again in the ostial LAD, in the same location as the beginning of the study. The balloon was inflated, and triphenyl tetrazolium chloride (TTC) was injected through the over the wire balloon. Simultaneously, Evans Blue dye was injected through the catheters into the right and left coronary arteries. The methods have been previously described by our group.^{19,20}

Echocardiograms were acquired at 1 hour and 4 hours in surviving animals. Blood samples were taken at baseline, every 5 minutes until ROSC, every 15 minutes until 60 minutes of CPR, and every hour after 60 minutes, or until the animal died.

Statistical analysis

Values were expressed as mean ± standard deviation. A two way ANOVA was used to evaluate lactic acid curves. Unpaired t-test was used to compare values from the two different groups of animals. A Kaplan-Meier Survival curve was used to assess survival at four hours. A p-value of <0.05 was considered significant.

RESULTS

CPR Hemodynamics

Animals in both groups had no difference in baseline hemodynamics and blood gasses. During BLS (up to the 10th minute of CPR) both groups had no differences in aortic pressure, systolic, diastolic, and in blood gasses, lactic acid and acidosis. During ACLS, coronary perfusion pressure was significantly higher after 30 minutes of CPR in the SNPeCPR group (Table 1).

Blood gasses, end-tidal CO₂ (ETCO₂) and lactic acid

SNPeCPR resulted in higher ETCO₂ levels during ACLS and significantly lower peak of lactic acid blood levels compared to controls (8.1 ± 3.2 versus 14.2 ± 3.3 $p=0.016$). In fact, lactic acid was significantly lower than control animals throughout the study after ACLS was initiated. (Figure 3)

Mean ETCO₂ was higher during ACLS with the SNPeCPR compared to controls (32 ± 8 mmHg versus 25 ± 5 , $p=0.03$). During the last 10 minutes of CPR before balloon deflation (30–40 minutes of CPR) the difference of mean ETCO₂ was accentuated between groups (28 ± 7 mmHg for SNPeCPR animals versus 11 ± 13 mmHg for controls, $p=0.01$). Blood gases showed differences in acidosis and base deficit as seen in Table 2.

Return of spontaneous circulation and defibrillation success

- a. **Stable ROSC within 60 min of resuscitation.** Eight out of 8 animals treated with SNPeCPR versus 2/8 control animals achieved ROSC within 60 minutes from initiation of CPR ($p=0.04$)
- b. **Defibrillation attempts until first ROSC.** Animals treated with SNPeCPR required significantly fewer defibrillation attempts before achieving first ROSC compared to control animals, 4.5 ± 2.7 versus 10.7 ± 6 respectively, $p=0.019$.
- c. **Recurrent CPR.** Total defibrillation attempts for recurrent VF/VT was similar in both groups (13 ± 11 versus 13.8 ± 8 $p=ns$) but the number of times reinitiating CPR after a defibrillation was significantly decreased with SNPeCPR compared to controls, 2 ± 1.2 versus 7.6 ± 7 respectively, $p=0.04$.

Four-hour survival

SNPeCPR improved 4-hour survival compared to control animals. The survival curves were significantly different as seen in Figure 4.

Four-hour LV function and infarct size

Baseline echocardiographic left ventricular ejection fraction was normal and similar between groups. No differences between groups could be analyzed due to the low number of animals that survived in the control group. Left ventricular ejection fraction at 4 hours post resuscitation was 34 ± 12 in the SNPeCPR group and 30% (1 animal) in the control group. Only SNPeCPR treated animals (6) could have their infarct to area at risk (AAR) evaluated

with TTC and Evans Blue. The average infarct/AAR area was $38 \pm 12\%$. One control animal was able to be evaluated and had an infarct/AAR of 42%.

DISCUSSION

Recent advances in clinical resuscitation options for patients with refractory cardiac arrest have shown that prolonged CPR resuscitation efforts are going to become more frequent.^{1,7,8,10,11} In Minnesota, the first community-wide refractory VF/VT protocol that focuses on early EMS mobilization to the CCL of patients with refractory OHCA has shown significant promise for improving survival.⁷ Preliminary experience indicates that the majority of the patients arriving at the hospital have already received 45–60 minutes of CPR with automated CPR devices. Achieving intermittent ROSC during EMS transport, the presence of lower lactic acid and higher ETCO₂ on arrival to the cardiac catheterization laboratory are all associated with functionally favorable survival.⁷ The vast majority of the patients presenting with refractory VF/VT have significant coronary pathology. The presence of reversible coronary lesions is also associated with better prognosis.⁷

We have therefore developed a new, reproducible translational porcine model of refractory ischemic VF to closely simulate the clinical reality of our refractory VF/VT patient population.⁷ Our animal model shows that ostial LAD occlusion with a large area of acute ischemia infrequently results in successful defibrillation and that prolonged CPR offers very little success in achieving ROSC and short term survival.

The data from this study support the hypothesis that improving perfusion with SNPeCPR ACLS promotes ROSC and leads to a significant increase in short term (4-hour) survival in our porcine model of refractory ischemic VF. The data demonstrate that after 20 minutes of on-going CPR, improving perfusion with SNPeCPR led to significantly lower lactic acid levels and higher ETCO₂. SNPeCPR also led to higher CPP values within 30 minutes of CPR despite the absence of epinephrine. This is consistent with our prior published work in prolonged resuscitation with open arteries where SNPeCPR led to higher carotid blood flow, 24-hour survival with good neurological function as well as significant improvement in post resuscitation left ventricular global function.^{13–17} In essence, we believe that the beneficial effects of SNPeCPR are mediated by an increase in “redirected” blood flow to the heart and brain and potentially through direct pharmacological effect of nitric oxide on the ischemic endothelium.

Prolonged resuscitation leads to accrual of ischemic injury and results in ischemic contracture of the heart that inevitably becomes unresponsive to defibrillation and resuscitation efforts.²¹ This is a time sensitive phenomenon.²¹ A CPR method that provides higher tissue perfusion may lead to better outcomes by delaying ischemic cardiac contracture.

As evident from the lactic acid levels, SNPeCPR-based ACLS, although better over a long period of resuscitation than standard ACLS, does not provide normal flow. Achieving ROSC was an obligatory condition to improve perfusion and decrease lactic acidosis to a survivable level during resuscitation. Therefore, achieving ROSC earlier and easier with SNPeCPR

offers a distinct advantage compared to current ALCS strategies. If ROSC is not achieved, the only current intervention with a reasonable expectation for survival is access to advanced perfusion therapies such as extracorporeal percutaneous membrane oxygenation (and its limited availability). Our collective data now suggest this is true regardless of the etiology of refractory VF (ischemic or non-ischemic).^{7,13–18}

The use of ACD+ITD and abdominal binding are crucial in the hemodynamic “rearrangement” of the arrested circulation in order to optimize flow during SNPeCPR. We have previously shown that the mechanical platform alone is better than STD CPR.¹⁵ ACD+ITD is necessary because it generates lower negative intrathoracic generation during the decompression phase and allows for “active” rather than “passive” venous return in a profoundly veno-dilated state in the presence of SNP. Abdominal binding is used to “mechanically” increase descending aortic resistance and promote cephalization of the circulating blood flow.

Our study has limitations. First, we did not test neurological outcome. We have previously shown in a similar non-ischemic model that prolonged resuscitation with SNPeCPR significantly improves 24-hour survival rates with favorable neurological function.¹³ Second, the effect in pigs may not be translated to humans. Third, our study cannot distinguish if the outcomes reported are due to a benefit of SNPeCPR or harm from the repeated epinephrine doses in the control group. A study to address this question is underway in our laboratory. Finally, our study cannot assess if the SNPeCPR effect is due to vasodilation or direct nitric oxide effect on the heart and vasculature. Mechanistic studies are needed to assess this as well as the use of other vasodilators in CPR on the same mechanical platform.

CONCLUSION

We have developed a new, reproducible, translational ischemic model of prolonged refractory VF arrest that can be used to simulate a clinical refractory VF/VT patient population. SNPeCPR based ACLS led to significantly higher rates of ROSC and 4-hour survival by improving intra-CPR perfusion. The benefits of SNPeCPR in humans deserve investigation.

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Figure 1. Study protocol

LAD: left anterior descending artery; VF: ventricular fibrillation; BLS: basic life support; CPR: cardiopulmonary resuscitation; SNPeCPR: Sodium nitroprusside enhanced CPR; ACLS: advanced cardiac life support; DC: direct current; J: joules; ROSC: return of spontaneous circulation

Figure 2. Left coronary artery angiograms

The two images on the left show a left coronary angiogram and ostial LAD occlusion from an Left Anterior Oblique 45° angle. An ostial LAD balloon inflation forms the basis of the severe refractory VF ischemic model. On the right we show an angiogram from a patient presenting with refractory VF in the CCL and ostial LAD occlusion. Red arrows show the LAD. LAD: left anterior descending artery.

Figure 3. Lactic acid Levels During the Course of the Study

The levels (mean $\pm$ SD) of arterial blood lactic acid are shown over the course of the study from the beginning of CPR. Significant lactic acid level differences were observed as early as 20 minutes of CPR. Decrease in lactic acid was only possible after ROSC was achieved. The numbers with the group's color demonstrate the number of animals alive at that time point in the protocol. SNPeCPR: sodium nitroprusside enhanced CPR; CPR: cardiopulmonary resuscitation; * denotes statistically significant differences.

Figure 4. Kaplan-Meier 4-hour Survival Curves

Survival curves for animals treated with standard and SNPeCPR ACLS are shown. Animals that were treated with SNPeCPR ACLS had a significant increase in 4-hours survival.

Table 1

Hemodynamic Parameters

Hemodynamic parameters between groups are shown over the duration of resuscitation.

	Baseline	10 min BLS	25 min ACLS	35 min	45 min	60 min	90 min ROSC
SNPeCPR							
SBP	91±11	30±16	74±31	79±9 *	70±15 *	72±14	79±7
DBP	60±7	26±6	55±23	52±11 *	47±13 *	48±11 *	54±6
RA	6±3	10±3	10±4	9±2	10±4	10±4	9±1
CPP	53±10	16±6	45±26	43±12 *	37±16	38±15 *	46±6
CONTROL							
SBP	88±16	39±20	83±60	52±24	46±26	50±31	
DBP	60±16	31±9	57±37	36±12	33±15	33±11	
RA	5±4	13±4	10±3	9±5	8±4	10±3	
CPP	52±19	17±10	46±39	28±16	31±19	24±21	

BL: baseline; BLS: basic life support; ACLS: advanced cardiac life support; ROSC: return of spontaneous circulation; SNPeCPR: sodium nitroprusside enhanced CPR; SBP: systolic blood pressure; DBP: diastolic blood pressure; RA: right atrial pressure; CPP: coronary perfusion pressure;

* means statistical significance.

Table 2

Arterial Blood Gases

Arterial blood gasses parameters between groups are shown over the duration of resuscitation.

	Baseline	10 min BLS	25 min ACLS	35 min ACLS	45 min	60 min
SNPeCPR						
pH	7.48±0.04	7.37±0.07	7.27±0.10	7.26±0.08	7.29±0.12	7.32±0.10
PCO ₂	40±4	40±10	44±13	43±8	45±6	45±6
PO ₂	103±13	206±75	163±40	176±113	227±81	202±94
HCO ₃	31±2	23±5	20±2	19±3	22±5	22±5
%SaO ₂	98±1	99±3	91±10	99±1	100±1	97±8
CONTROL						
pH	7.48±0.07	7.36±0.12	7.31±0.11	7.25±0.14	7.28±0.13	7.24±0.16
PCO ₂	41±9	31±7	27±9 *	36±7 *	30±12 *	29±12 *
PO ₂	105±17	241±86	189±63	151±80	189±89	135±66
HCO ₃	30±2	18±6	13±4 *	14±4 *	13±3 *	11±3 *
%SaO ₂	98±2	99±1	99±3	94±9	97±7	94±10

BLS: Basic Life support; ACLS: Advanced cardiac life support.

* means statistical significance.