Controlled pauses at the initiation of sodium nitroprusside-enhanced cardiopulmonary resuscitation facilitate neurological and cardiac recovery after 15 mins of untreated ventricular fibrillation

Demetris Yannopoulos, MD; Nicolas Segal, MD; Scott McKnite, BS; Tom P. Aufderheide, MD; Keith G. Lurie, MD

Objective: A multipronged approach to improve vital organ perfusion during cardiopulmonary resuscitation that includes sodium nitroprusside, active compression-decompression cardiopulmonary resuscitation, an impedance threshold device, and abdominal pressure (sodium nitroprusside-enhanced cardiopulmonary resuscitation) has been recently shown to increase coronary and cerebral perfusion pressures and higher rates of return of spontaneous circulation vs. standard cardiopulmonary resuscitation. To further reduce reperfusion injury during sodium nitroprusside-enhanced cardiopulmonary resuscitation, we investigated the addition of adenosine and four 20-sec controlled pauses spread throughout the first 3 mins of sodium nitroprusside-enhanced cardiopulmonary resuscitation. The primary study end point was 24-hr survival with favorable neurologic function after 15 mins of untreated ventricular fibrillation.

Design: Randomized, prospective, blinded animal investigation.

Setting: Preclinical animal laboratory.

Subjects: Thirty-two female pigs (four groups of eight) 32 ± 2 kg.

Interventions: After 15 mins of untreated ventricular fibrillation, isoflurane-anesthetized pigs received 5 mins of either standard cardiopulmonary resuscitation, sodium nitroprusside-enhanced cardiopulmonary resuscitation, sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine, or controlled pauses-sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine. After 4 mins of cardiopulmonary resuscitation, all animals received epinephrine (0.5 mg) and a defibrillation shock 1 min later. Sodium nitroprusside-enhanced cardiopulmonary resuscitation-treated animals received sodium nitroprusside (2 mg) after 1 min of cardiopulmonary resuscitation and 1 mg after 3 mins of cardiopulmonary resuscitation. After 1 min of sodium nitroprusside-enhanced cardiopulmonary resuscitation, adenosine (24 mg) was administered in two groups.

Measurements and Main Results: A veterinarian blinded to the treatment assigned a cerebral performance category score of 1–5 (normal, slightly disabled, severely disabled but conscious, vegetative state, or dead, respectively) 24 hrs after return of spontaneous circulation. Sodium nitroprusside-enhanced cardiopulmonary resuscitation, sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine, and controlled pauses-sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine resulted in a significantly higher 24-hr survival rate compared to standard cardiopulmonary resuscitation (7 of 8, 8 of 8, and 8 of 8 vs. 2 of 8, respectively p < .05). The mean cerebral performance category scores for standard cardiopulmonary resuscitation, sodium nitroprusside-enhanced cardiopulmonary resuscitation, sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine, or controlled pauses-sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine were 4.6 ± 0.7, 3 ± 1.3, 2.5 ± 0.9, and 1.5 ± 0.9, respectively (p < .01 for controlled pauses-sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine compared to all other groups).

Conclusions: Reducing reperfusion injury and maximizing circulation during cardiopulmonary resuscitation significantly improved functional neurologic recovery after 15 mins of untreated ventricular fibrillation. These results suggest that brain resuscitation after prolonged cardiac arrest is possible with novel, noninvasive approaches focused on reversing the mechanisms of tissue injury. (Crit Care Med 2012; 40:1562–1569)

Key Words: active compression-decompression cardiopulmonary resuscitation; adenosine; cardiopulmonary resuscitation; impedance threshold device; left ventricular function; neurological function; reperfusion injury; sodium nitroprusside; survival

From the Cardiovascular Division (DY, KGL), Department of Emergency Medicine (SM, NS, KGL), University of Minnesota, Minneapolis, MN; and the Department of Emergency Medicine (TPA), Medical College of Wisconsin, Milwaukee, WI.

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For information regarding this article, E-mail: yanno001@umn.edu

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Cardiopulmonary resuscitation (CPR) rates have remained poor over the past half century, with only minimal if any improvements in neurologically intact survival (1). Clinical studies have historically demonstrated that when ventricular fibrillation (VF) is untreated for >10 mins, short- and long-term survival is severely reduced (2). In animal models, current noninvasive methods of resuscitating untreated ventricular fibrillation of durations longer than 12–13 mins prohibit short- and long-term neurologic recovery (3–5). Successful resuscitation after 12–15 mins of untreated VF has been used as the model to evaluate postresuscitation left ventricular dysfunction, which manifests as global hypokinesis and moderate decreases in left ventricular ejection fraction that are obvious within the first hour and continue to decline up to 4 hrs post resuscitation (6).

Sodium nitroprusside (SNP) “enhanced”-CPR, or SNPeCPR, is a method of resuscitation that consists of: 1) active compression-decompression (ACD) CPR with an impedance threshold device, which improves vital organ blood flow, and improves short- and long-term survival compared to standard CPR in both animal and human studies (7–9); 2) manual lower abdominal binding, which mechanically increases resistance to descending aortic blood flow and augments venous blood return to the heart, thereby effectively redistributing blood flow (10, 11); and 3) high-dose intravenous boluses of SNP, which vasodilates coronary and cerebral vascular beds and decreases peripheral vascular resistance to the heart and brain (12, 13).

Recent animal studies have demonstrated that SNPeCPR can maintain heart and brain viability and significantly improve carotid blood flow (CBF), end-tidal CO₂ (ETCO₂), and return of spontaneous circulation (ROSC) and 24-hr survival rates with favorable neurologic function compared to standard CPR after 8 mins of untreated VF and with up to 25 mins of CPR (12). Furthermore, SNPeCPR use has resulted in a >90% ROSC rate after 15 mins of untreated VF and pulseless electrical activity arrest (13). SNPeCPR significantly improved outcomes in the same animal model when compared to the 2010 American Heart Association resuscitation recommendations (standard CPR) ACLS protocol (13).

Recognizing that heart and brain recovery after a prolonged ischemic insult may depend upon physiologic processes independent of coronary and cerebral perfusion, in the current investigation we focused on novel ways to protect the heart and brain from ischemia-reperfusion injury. Building upon our recent studies with SNPeCPR and recent findings by others in models of regional myocardial and cerebral ischemia (12–16), in this study we tested two new strategies aimed at improving neurologic and myocardial function after prolonged cardiac arrest. Those strategies include: 1) addition of a large bolus of adenosine in addition to the SNP bolus at the initiation of CPR, since adenosine has been shown to have cardiac protective effects after ischemia both in animals and humans (17–20); and 2) controlled introduction of blood flow with a “stuttering” manner by providing intermittent 20-sec pauses in chest compressions and ventilations (controlled pauses: CPs) throughout the first 3 mins of reperfusion. “Stuttering” reintroduction of blood flow has been shown to protect the myocardium and the brain from ischemia-reperfusion injury in clinical scenarios of regional ischemia during ST-elevation myocardial infarction and stroke both in animals and humans (21–24).

We hypothesized that the combination of the above strategies will provide cerebral and myocardial protection against reperfusion injury and facilitate functional recovery. The purpose of this study, then, was to evaluate hemodynamics, acid-base status, rates of ROSC, and 24-hr survival, as well as left ventricular function and 24-hr neurologic recovery in pigs with 15 mins of untreated VF resuscitated with different multipronged reperfusion injury protection strategies (SNPeCPR + adenosine; CP-SNPeCPR + adenosine) vs. SNPeCPR alone and standard CPR.

**MATERIALS AND METHODS**

All studies were performed by a qualified, experienced research team in Yorkshire female farm pigs weighing 32 ± 2 kg. A certified and licensed veterinarian provided a blinded neurologic assessment at 24 hrs. The protocol was approved by the Institutional Animal Care Committee of the Minneapolis Medical Research Foundation of Hennepin County Medical Center. All animal care was compliant with the National Research Council’s 1996 Guidelines for the Care and Use of Laboratory Animals.

**Preparatory Phase**

The anesthesia, surgical preparation, data monitoring, and recording procedures used in this study have been described previously (25). Briefly, we employed aseptic surgical conditions, using initial sedation with intramuscular ketamine (7 mL of 100 mg/mL, Ketaset, Fort Dodge Animal Health, Fort Dodge, IA) followed by inhaled isoflurane at a dose of 0.8% to 1.2%. Pigs were intubated with a size 7.0 endotracheal tube. The animal’s bladder temperature was maintained at 37.5 ± 0.5°C with a warming blanket (Bair Hugger, Augustine Medical, Eden Prairie, MN). Central aortic blood pressure was recorded continuously with a micromanometer-tipped (Mikro-Tip Transducer, Millar Instruments, Houston, TX) catheter placed at the beginning of the descending thoracic aorta. A second Millar catheter was inserted in the right atrium via the right external jugular vein. All animals received an intravenous heparin bolus (100 units/kg) and 500 units of heparin every hour until surgical repair was completed. An ultrasound flow probe (Transonic 420 series multichannel, Transonic Systems, Ithaca, NY) was placed to the right internal carotid artery to record blood flow (mL/min). The animals were then ventilated with room air, using a volume-control ventilator (Narcomed, Telford, PA), with a tidal volume of 10 mL/kg and a respiratory rate adjusted to continually maintain a Paco₂ of 40 mm Hg and Pao₂ of 80 mm Hg (blood oxygen saturation >95%), as measured from arterial blood (Gem 3000, Instrumentation Laboratory, Lexington, MA) to adjust the ventilator as needed. Surface electrocardiographic tracings were continuously recorded. All data were recorded with a digital recording system (BIOPAC MP 150, BIOPAC Systems, CA). ETCO₂, tidal volume, minute ventilation, and blood oxygen saturation were continuously measured with a respiratory monitor (CO₂SMO Plus, Novametrix Medical Systems, Wallingford, CT).

**Measurements and Recording**

Thoracic aortic pressure, right atrial pressure, ETCO₂, and CBF were continuously recorded. Coronary perfusion pressure during CPR was calculated from the mean arithmetic difference between right atrial pressure and aortic pressure during the decompression phase. Carotid artery blood flow was reported in mL/sec.

**Experimental Protocol**

After the surgical preparation was complete, oxygen saturation on room air was >95%, and ETCO₂ was stable between 35 and 42 mm Hg for 5 mins. VF was induced by delivering direct intracardiac current via...
a temporary pacing wire (St. Jude Medical, Minnetonka, MN). The ventilator tube was disconnected from the endotracheal tube. Standard and ACD CPR were performed with a pneumatically driven automatic piston device (Pneumatic Compression Controller, Ambu International, Glostrup, Denmark) as previously described (26). During standard CPR, uninterupted chest compressions were performed at a rate of 100 compressions/min, with a 50% duty cycle and a compression depth of 25% of the anteroposterior chest diameter were provided. With ACD-CPR, the chest was actively pulled upwards after each compression with a decompression force of 60 lbs. Simultaneous with ACD-CPR an impedance threshold device (ResQPOD™, Advanced Circulatory Systems, Roseville, MN) with a resistance of 27 mm Hg was attached to the endotracheal tube. In addition, during SNPeCPR, manual abdominal binding was performed to provide approximately 40 lbs of force as previously described (12, 13). During both standard and ACD CPR, asynchronous positive-pressure ventilations were delivered with room air (FIO2 of 0.21) with a manual resuscitator bag. The tidal volume was maintained at —10 mL/kg and the respiratory rate was 10 breaths/min. The investigators were blinded to hemodynamics during CPR.

Protocol

Following 15 mins of untreated VF, 32 pigs were randomized to either 5 mins of: 1) standard CPR; 2) SNPeCPR; 3) SNPeCPR + adenosine; or 4) CP-SNPeCPR + adenosine (four groups of eight animals) before the first defibrillation attempt. Epinephrine was administered in all groups in a 0.5-mg (—15 µg/kg) bolus at minute 4 whereas SNP was delivered into the jugular vein in the SNPeCPR, SNPeCPR + adenosine, and CP-SNPeCPR + adenosine groups as a 2-mg bolus at minute 1 and a second 1-mg bolus at minute 3 of CPR. In the last two groups, adenosine was administered as a single 24-mg intravenous bolus after the first SNP bolus.

The eight animals randomized to receive CPs had 40 secs of SNPeCPR and then received 2 mg of SNP and 24 mg of adenosine. This was followed by four cycles of a 20-sec pause and 20 secs of SNPeCPR, until the end of the third minute of CPR. Then animals received uninterrupted SNPeCPR until defibrillation (Figure 1). A bolus of 24 mg of adenosine (compared to 12 mg) was chosen because in our preliminary studies, it significantly increased CBF during CPR and the effect was longer lasting, extending into the postresuscitation period.

Resuscitation efforts were continued until ROSC was achieved or a total of 15 mins of CPR had occurred. Defibrillation was delivered with 150-J biphasic shocks after 5 mins of CPR. If ROSC was not achieved, defibrillation was delivered every 2 mins thereafter during CPR.

Post-ROSC Care

After ROSC was achieved, animals were connected to the mechanical ventilator. Supplemental oxygen was added only if arterial saturation was lower than 90%. Animals were observed under general anesthesia with isoflurane until hemodynamically stable. Hemodynamic stability was defined as a mean aortic pressure >55 mm Hg without pharmacologic support for 10 mins and normalization of ETCO2, and acidosis. Animals that had a stable post-ROSC rhythm but were hypotensive (mean arterial pressure <50 mm Hg) received 1000 mL of intravenous normal saline bolus over 60 mins. If mean arterial pressure was still <50 mm Hg, they received increments of 0.1–0.2 mg intravenous epinephrine every 5 mins until mean arterial pressure rose above 50 mm Hg. If pH was lower than 7.2, 50–100 mEq of NaHCO3 were given intravenously. This was repeated as needed for significant acidosis. At that point, vascular repair of the internal jugular and the left common femoral artery were then performed. Arterial blood gases were obtained at baseline, at 5 mins of CPR, and every 30 mins following ROSC.

Survivors were given intramuscular analgesic injections of nonsteroidal anti-inflammatory medication as previously described and had free access to water and food (26). There was no other post-ROSC medical care provided after the vascular repair. Animals were returned to their runs and were observed every 2 hrs for the first 6 hrs for signs of distress or accelerated deterioration of their function. If animals met predetermined criteria or if the veterinarian judged that they were in severe distress they were euthanized per Institutional Animal Care and Use Committee protocol.

Neurologic Assessment

Twenty-four hours after ROSC, a certified veterinarian, blinded to the intervention, assessed the pigs’ neurologic function based on a cerebral performance category (CPC) scoring system modified for pigs. The veterinarian used clinical signs, such as response to opening the cage door, response to noxious stimuli if unresponsive, response to trying to lift the pig, whether the animal could stand, move all four limbs, walk, eat, urinate, defecate, and respond appropriately to the presence of a person walking into the cage. The following scoring system was used: 1 = normal; 2 = slightly disabled; 3 = severely disabled but conscious; 4 = vegetative state; 5 = given to animals that died in the lab due to unachievable ROSC or died in the cage following ROSC (26). A dichotomous assessment of good (CPC ≤2) vs. poor (CPC >2) outcomes was also evaluated. Except the veterinarian, postresuscitation care was not blinded since

Figure 1. Controlled-pauses (CP-) protocol during sodium nitroprusside-enhanced cardiopulmonary resuscitation (SNPeCPR). In the CP-SNPeCPR + adenosine group during the first 3 mins of SNPeCPR, animals received four 20-sec pauses and each pause was followed by 20 secs of SNPeCPR. That “stuttering” introduction of reperfusion is called “controlled pauses.” VF, ventricular fibrillation; ROSC, return of spontaneous circulation; SNP, sodium nitroprusside.
Table 1. Hemodynamics, resuscitation rates, and left ventricular ejection fraction

<table>
<thead>
<tr>
<th>CPR Method</th>
<th>Measurement</th>
<th>Baseline</th>
<th>2-min CPR</th>
<th>5-min CPR</th>
<th>1-hr ROSC</th>
<th>4-hr ROSC</th>
<th>Number of Shocks to Initial ROSC</th>
<th>Post-ROSC Epinephrine Dose</th>
<th>ROSC</th>
</tr>
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<tr>
<td>Standard CPR</td>
<td>SBP</td>
<td>82 ± 6</td>
<td>48 ± 3</td>
<td>76 ± 5</td>
<td>86 ± 7</td>
<td>78 ± 8</td>
<td>6 ± 2</td>
<td>2.2 ± 1.2</td>
<td>5</td>
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<tr>
<td></td>
<td>DBP</td>
<td>60 ± 3</td>
<td>18 ± 5</td>
<td>31 ± 4</td>
<td>57 ± 11</td>
<td>61 ± 9</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>RA</td>
<td>3 ± 2</td>
<td>2 ± 1</td>
<td>2 ± 3</td>
<td>0.5 ± 2</td>
<td>4 ± 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPP</td>
<td>57 ± 6</td>
<td>16 ± 4</td>
<td>29 ± 3</td>
<td>57 ± 8</td>
<td>57 ± 4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>CBF</td>
<td>186 ± 36</td>
<td>35 ± 15</td>
<td>18 ± 6</td>
<td>115 ± 26</td>
<td>137 ± 16</td>
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<tr>
<td></td>
<td>LVEF%</td>
<td>60 ± 12</td>
<td>N/A</td>
<td>N/A</td>
<td>31 ± 9</td>
<td>28 ± 10</td>
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<tr>
<td>SNPeCPR</td>
<td>SBP</td>
<td>87 ± 5</td>
<td>65 ± 3²</td>
<td>110 ± 4²</td>
<td>83 ± 8</td>
<td>76 ± 4</td>
<td>3 ± 4</td>
<td>0.7 ± 0.6²</td>
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<td></td>
<td>DBP</td>
<td>56 ± 7</td>
<td>27 ± 6³</td>
<td>39 ± 4²</td>
<td>63 ± 6</td>
<td>29 ± 4³</td>
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<tr>
<td></td>
<td>RA</td>
<td>3 ± 2</td>
<td>8 ± 4²</td>
<td>6 ± 3</td>
<td>1 ± 3</td>
<td>4 ± 2</td>
<td></td>
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<tr>
<td></td>
<td>CPP</td>
<td>53 ± 4</td>
<td>20 ± 5²</td>
<td>33 ± 4</td>
<td>61 ± 5</td>
<td>23.2 ± 4²</td>
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<td></td>
<td>CBF</td>
<td>176 ± 48</td>
<td>158 ± 25²</td>
<td>86 ± 26²</td>
<td>183 ± 34³</td>
<td>163 ± 43</td>
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<tr>
<td></td>
<td>LVEF%</td>
<td>62 ± 8</td>
<td>N/A</td>
<td>N/A</td>
<td>53 ± 12</td>
<td>55 ± 9</td>
<td>3 ± 3</td>
<td>0.6 ± 0.8²</td>
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<td>SNPeCPR 1 adenosine</td>
<td>SBP</td>
<td>91 ± 5</td>
<td>77 ± 3²</td>
<td>122 ± 9</td>
<td>86 ± 9</td>
<td>76 ± 9</td>
<td>3 ± 3</td>
<td>0.6 ± 0.8²</td>
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<tr>
<td></td>
<td>DBP</td>
<td>64 ± 4</td>
<td>26 ± 2²</td>
<td>40 ± 6²</td>
<td>71 ± 7</td>
<td>62 ± 7</td>
<td></td>
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<tr>
<td></td>
<td>RA</td>
<td>2 ± 2</td>
<td>6 ± 1³</td>
<td>4 ± 4</td>
<td>1 ± 2</td>
<td>5 ± 3</td>
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<td>CPP</td>
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<td>24 ± 3³</td>
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<td>70 ± 7</td>
<td>57 ± 6</td>
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<tr>
<td></td>
<td>CBF</td>
<td>181 ± 25</td>
<td>189 ± 55³</td>
<td>133 ± 44³</td>
<td>333 ± 88³</td>
<td>275 ± 62³</td>
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<tr>
<td></td>
<td>LVEF%</td>
<td>60 ± 13</td>
<td>N/A</td>
<td>N/A</td>
<td>72 ± 10³</td>
<td>77 ± 13³</td>
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<tr>
<td>Controlled pauses-SNPeCPR + adenosine</td>
<td>SBP</td>
<td>87 ± 5</td>
<td>57 ± 7</td>
<td>156 ± 11³</td>
<td>88 ± 11</td>
<td>86 ± 13</td>
<td>2 ± 1</td>
<td>0.2 ± 0.2³²³</td>
<td>8</td>
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<tr>
<td></td>
<td>DBP</td>
<td>62 ± 4</td>
<td>28 ± 2³</td>
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<td></td>
<td>RA</td>
<td>3 ± 2</td>
<td>5 ± 2</td>
<td>6 ± 7³</td>
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<td></td>
<td>CPP</td>
<td>59 ± 3</td>
<td>23 ± 5³</td>
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<td>62 ± 4</td>
<td></td>
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<tr>
<td></td>
<td>CBF</td>
<td>173 ± 37²</td>
<td>228 ± 25³</td>
<td>128 ± 47³</td>
<td>403 ± 76³</td>
<td>193 ± 59³</td>
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<tr>
<td></td>
<td>LVEF%</td>
<td>58 ± 11</td>
<td>N/A</td>
<td>N/A</td>
<td>79 ± 7³</td>
<td>80 ± 7³</td>
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</table>

CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; SBP, systolic blood pressure; DBP, diastolic blood pressure; RA, right atrial pressure; CPP, coronary perfusion pressure; CBF, carotid blood flow; LVEF, left ventricular ejection fraction; N/A, not applicable; SNPeCPR, sodium nitroprusside-enhanced CPR.

Values are shown as mean ± sd. CPR was performed with standard CPR, SNPeCPR, SNPeCPR + adenosine, or controlled pauses-SNPeCPR + adenosine. All pressures are in mm Hg, all flows in mL/min. *a-b-c mean statistically significant difference compared to S-CPR, SNPeCPR and SNPeCPR + adenosine, respectively.

the same team performed CPR and provided post-ROSC care.

Echocardiographic Evaluation of Left Ventricular Function

A transthoracic echocardiogram was obtained on all survivors 1 and 4 hrs post ROSC. Images were obtained from the right parasternal window, which provides similar views as the long and short parasternal windows in humans (27). Ejection fraction was assessed using Simpson’s method of volumetric analysis by an independent clinical echocardiographer blinded to the treatments (28). Before echocardiographic evaluation, any inotropic support was stopped for at least 20 mins and, if needed, was restarted immediately after the echocardiographic evaluation.

Statistical Analysis

Values are expressed as mean ± sd. Baseline data, hemodynamic parameters, and blood gases during and after CPR were analyzed with two-way analysis of variance. Pairwise comparison of subgroups was performed with the Student Newman-Keuls test. A two-tailed Fisher’s exact test was used to compare 24-hr survival rate. A t test was used to evaluate mean CPC scores between groups. The primary study end point was survival with a favorable neurologic function 24 hrs after ROSC, as determined by a CPC score of <3. A p value of <.05 was considered statistically significant.

RESULTS

There were no significant baseline differences between treatment groups in any hemodynamic or respiratory parameters (Tables 1 and 2).

CPR Hemodynamics

SNPeCPR provided significantly higher internal CBF during CPR compared to standard CPR in all animals. Addition of adenosine to SNPeCPR significantly increased CBF compared to SNPeCPR alone both during CPR and especially after ROSC (Table 1).

Animals that received CP-SNPeCPR + adenosine had higher arterial blood pressure (156 ± 11/72 ± 4 mm Hg) and coronary perfusion pressure (66 ± 4 mm Hg) after 5 mins of CPR compared to all other groups. The effect of epinephrine in the animals that received CP-SNPeCPR + adenosine was pronounced and the aortic pressure and coronary perfusion pressures were increased to normal or higher than normal resting values (Table 1).

In the animals that received CP-SNPeCPR + adenosine, CBF during the pauses was essentially zero and during CPR ranged from 128 ± 47 mL/sec to 228 ± 25 mL/sec, as seen in Table 1.

ROSC and 24-hr Survival

There were no significant differences in ROSC between groups (Table 1). In the standard CPR group, five of eight animals achieved ROSC, and two of eight animals survived 24 hrs. In the SNPeCPR group, seven of eight animal had initial ROSC and survived to 24 hrs (p = .04 for 24-hr survival rate compared to standard CPR). In the SNPeCPR + adenosine and CP-SNPeCPR + adenosine groups, eight of eight and eight of eight animals had ROSC and survived to 24 hrs (p = .007 for 24-hr survival rate compared to standard CPR for both groups, respectively) (Fig. 2). Animals in the SNPeCPR groups were significantly more stable hemodynamically and therefore received significantly
less epinephrine than those in the standard CPR group during the recovery period (Table 1). Three of the five animals treated with standard CPR and had ROSC were unstable and died during the night.

Table 2. Arterial blood gases during cardiopulmonary resuscitation and after return of spontaneous circulation

<table>
<thead>
<tr>
<th>CPR Method</th>
<th>Measurement</th>
<th>Baseline</th>
<th>5-min CPR</th>
<th>30-min Return of Spontaneous Circulation</th>
<th>4-hr Return of Spontaneous Circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard CPR</td>
<td>pH</td>
<td>7.39 ± 0.04</td>
<td>7.22 ± 0.07</td>
<td>7.23 ± 0.04</td>
<td>7.33 ± 0.01</td>
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<tr>
<td></td>
<td>Pco₂</td>
<td>42 ± 3</td>
<td>38 ± 2</td>
<td>39 ± 1</td>
<td>33 ± 1</td>
</tr>
<tr>
<td></td>
<td>Po₂</td>
<td>96 ± 5</td>
<td>76 ± 3</td>
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<td></td>
<td>HCO₃⁻</td>
<td>23 ± 5</td>
<td>16 ± 2</td>
<td>18 ± 2</td>
<td>18 ± 4</td>
</tr>
<tr>
<td></td>
<td>ETCO₂</td>
<td>40 ± 2</td>
<td>19 ± 3</td>
<td>37 ± 7</td>
<td>42 ± 3</td>
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<td>SNPeCPR</td>
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<td>7.19 ± 0.08</td>
<td>7.28 ± 0.04</td>
<td>7.31 ± 0.01</td>
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<td>47 ± 5</td>
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<td>Po₂</td>
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<td>84 ± 16</td>
<td>98 ± 6</td>
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<tr>
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<td></td>
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<td>SNPeCPR + adenosine</td>
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<tr>
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CPR, cardiopulmonary resuscitation; HCO₃⁻, bicarbonate; ETCO₂, end-tidal CO₂; SNPeCPR, sodium nitroprusside-enhanced CPR.

Mean ± SD. Arterial blood gas measurements at baseline, during CPR, and after return of spontaneous circulation. Partial pressures in torr. * ‡ § mean statistically significant difference compared to standard CPR, SNPeCPR, and SNPeCPR + adenosine, respectively.

Figure 2. Twenty-four-hour neurologic assessment. Sodium nitroprusside-enhanced cardiopulmonary resuscitation (SNPeCPR) significantly improved neurologic function compared to standard cardiopulmonary resuscitation (S-CPR). The addition of adenosine to SNPeCPR did not significantly improve neurologic function further compared to SNPeCPR alone. Finally, the controlled pauses SNPeCPR (CP-SNPeCPR) + adenosine (four 20-sec pauses) group had six of eight animals that were blindly scored as normal (cerebral performance category of 1) and significantly improved compared to all other groups. Cerebral performance category score: 1 = normal, 2 = mild deficit, 3 = severe deficit, 4 = coma, 5 = dead. * ‡ § mean statistically significant difference compared to standard CPR, SNPeCPR, and SNPeCPR + adenosine respectively.

Left Ventricular Function

Echocardiographic evaluation at 1 hr revealed that animals receiving SNPeCPR alone had a significantly higher left ventricular ejection fraction than those animals treated with standard CPR (53% ± 12% vs. 31% ± 9%, p < .001). The effect was maintained at 4 hrs (55% ± 9% vs. 28% ± 10%, p = .001). Addition of adenosine to SNPeCPR alone resulted in hyperdynamic function (72% ± 10% and 77% ± 13% at 1 and 4 hrs, respectively, p < .001 compared with standard CPR and SNPeCPR for both time points). Left ventricular ejection fraction was also hyperdynamic and not significantly different in the animals that received CP-SNPeCPR + adenosine (79% ± 7% and 80% ± 7%, at 1 and 4 hrs, respectively) compared to animals that received SNPeCPR + adenosine (Table 1).

Neurologic Function at 24 Hrs

The number of pigs with good neurologic function was significantly higher in the animals that received CP-SNPeCPR + adenosine compared to all other groups (Fig. 2). Two animals that received standard CPR and survived to 24 hrs had CPC scores of 3 and 4 (coma), respectively. The 24-hr neurologic outcome (CPC scores) did not differ significantly between the animals that received SNPeCPR and SNPeCPR + adenosine, but both groups were significantly better than standard CPR (p < .008 and p < .0001, respectively). Animals that additionally received four 20-sec CPs during the first 3 mins of CPR (CP-SNPeCPR + adenosine), demonstrated significant
improvement in their neurologic function and six of eight were scored with a CPC of 1 ($p < .001$ compared with standard CPR, $p = .009$ compared with SNPeCPR, and $p = .01$ compared with SNPeCPR + adenosine). Nearly all animals had a left hind leg weakness during walking that was not scored since it was coexistent with the site of the femoral artery cut down and femoral nerve trauma (Fig. 2).

**Blood Gas and ETCO2**

There were no significant differences in blood gas values at baseline between groups. After 5 mins of CPR there were no significant differences in blood gases except for a significantly lower arterial pH in the SNPeCPR + adenosine group. ETCO2 was significantly lower in the standard CPR group compared to all other groups after 5 mins of CPR. Thirty minutes post ROSC, the animals in the CP-SNPeCPR + adenosine group had normalized their blood gases whereas the arterial pH values in all other groups remained significantly lower (Table 2).

**DISCUSSION**

In this investigation, a novel strategy to reduce ischemia-reperfusion injury was combined with SNPeCPR and implemented in pigs after 15 mins of untreated VF. This new approach resulted in complete neurologic recovery in six of eight pigs and a substantial reduction in postresuscitation left ventricular dysfunction. To our knowledge this is the first time that survival rates with consistently favorable neurologic outcomes have been reported using the combination of noninvasive techniques and pharmacologic therapies after 15 mins of untreated cardiac arrest.

This study focused on two critical physiologic targets for improving resuscitation outcome. First, a new CPR technique was implemented to increase ROSC rates by enhancing circulation and perfusion. Without ROSC, any other strategy to mitigate injury is futile. Second, we implemented an innovative method to minimize the injury that is inevitably caused by reintroduction of flow to ischemic tissues (16, 22).

SNPeCPR was used to augment circulation and vital organ perfusion. With this approach, ROSC rates were nearly 100% in the SNPeCPR group, but favorable neurologic recovery was only observed in half the animals. The addition of exogenous adenosine was chosen to minimize impairment because it has been shown to offer myocardial and cerebral protection from ischemia reperfusion injury. Multiple studies have shown that when adenosine is given during reperfusion of ST-elevation myocardial infarction, it provides reperfusion injury protection, infarct size is significantly reduced, and microcirculation reactivity is protected (17–20). Similar but less clear outcomes have been shown for cerebral protection in stroke from ischemia and reperfusion (29–31). Our results suggest that the addition of adenosine to SNPeCPR eliminated postresuscitation myocardial dysfunction since the ventricles were shown to be hyperdynamic in the absence of inotropic medications. Addition of adenosine alone, however, did not significantly alter neurologic function in this study, although a relative contribution cannot be excluded since the study was not powered or designed to address this question.

The implementation of four CPs of the chest compressions and ventilations at the start of SNPeCPR was used to decrease reperfusion injury. This new intervention consistently resulted in clinically measurable and relevant neurologic recovery in the absence of prolonged intensive care or therapeutic hypothermia. CPs provide a “stuttering” introduction of blood flow: repeated 20-sec pauses followed by 20 secs of CPR were used only during the first 3 mins after CPR initiation. While this new approach may appear to be antithetical to current thinking that continuous uninterrupted chest compressions are an essential element of modern CPR, three to four pauses of 15–20–sec duration during the first 3 mins after CPR initiation followed by continuous chest compressions with asynchronous ventilations for the remainder of the resuscitation appeared to positively impact neurologic outcome after very prolonged global cerebral ischemia.

The supporting evidence that short duration pauses of blood flow during the first several minutes of reperfusion are beneficial for organ preservation is extensive both in the cardiology and, more recently, in neurology literature. Pauses during reperfusion of acute myocardial infarction have been shown to significantly decrease infarct size (22, 23). Stutter reperfusion with 15–20–sec pauses at the initiation of reperfusion of stroke has been shown to significantly decrease injury in a rat model (32). Furthermore, 15-sec cycles of on/off flow in the same model with 10 mins of global ischemic cerebral insult have provided significant cerebral preservation and recovery (32). The latter model is relevant to cardiac arrest where the ischemic insult is systemic and global. These mechanisms for protection of both the heart and brain have been well studied and are currently considered to be mediated by mitochondrial protection (15).

In all studies where stutter flow has been shown to be beneficial and protective from regional ischemia/reperfusion injury, the duration of ischemia (absence of flow before reperfusion) was significantly longer than 15 mins (16, 22). Although systemic ischemia during cardiac arrest is considered a severe and global insult, the potential for recovery of the individual organs may also be greater since the average ischemic time (no flow) in cardiac arrest (<15 mins) is less than the ischemic time during myocardial (<4 hrs) or cerebral infarction (<3 hrs) where the pauses in reperfusion have shown benefit (16, 22).

This study shows that controlled, intentional cycles of CPR/pauses for the first 3 mins was associated with significant improvements in neurologic and cardiac recovery. The significant improvement observed in neurologic outcomes with the introduction of mechanical reperfusion injury protection suggests that this strategy is critical in decreasing the injury of reperfusion following untreated cardiac arrest after initiation of CPR. Generation of flow also does not appear as critical during the first 3 mins of resuscitation, but becomes more significant later to achieve ROSC. It is important to emphasize that unintentional pauses in chest compressions spread throughout resuscitative efforts have been associated with worse outcomes by adding to the injury that has accumulated from the no-flow period (33–35). The type of intentional pauses described in this report is thought to harness endogenous repair processes associated with specific mitochondrial protective mechanics (15) and should not be confused with the poor outcomes known to be associated with poor CPR quality that includes prolonged intervals of interrupted chest compressions. In addition, the pauses here should not be confused with the unintentional pauses that happen with the change of rescuers providing compressions during CPR. The CPs described here occur at the initiation of
CPR and only for the first 3 mins of CPR. They last for 20 secs and are followed by short duration of CPR (another 20 secs) in well-defined cycles up until the third minute of CPR.

This study has limitations. Rather than determine the potential individual contributions of the two new interventions, adenosine and interruptions in chest compression, we intentionally built upon recent advances with SNPeCPR. Since we added CPs to SNPeCPR and adenosine, we cannot yet distinguish the relative contribution of the components to final neurologic recovery. Synergy between the pharmacologic agents and the mechanical intervention is also possible. New studies are currently investigating the relative contribution of each of these resuscitation components, focusing on markers of mitochondrial protection/injury as well as magnetic resonance imaging/histopathology of the brain to correlate the observed clinical neurologic findings with the pathophysiology and pathology of injury evolution. Second, we did not add CPs to standard CPR and therefore we cannot comment at this time on its potential effect in this setting. In addition, we did not test the dosing of adenosine and the CPs. Third, we neither assessed biomarkers of injury for the heart and brain, nor investigated mechanisms in this first report on using CPs during CPR. Although the clinical end points reported here, in our opinion, represent higher quality preclinical end points than biomarkers, we do not yet know the biochemical processes underlying the tissue protection despite the observed improvement in myocardial and cerebral outcome. We speculate that the protection offered by CPs and adenosine should have similar underlying mechanisms to the ones documented in the acute myocardial infarction and stroke literature (16, 22). However, we tested those interventions exactly as described for acute myocardial infarction and stroke and found them to be extremely effective in our model of cardiac arrest (16, 22). It is also unknown if the benefits demonstrated in this study would be seen with coexisting myocardial ischemia or can be translated to humans. Finally, in our model, we used intravenous heparin that was necessary to avoid sheath and catheter thrombosis during the long untreated VF, which could be a confounding factor.

CONCLUSION
We report high rates of functional neurologic and left ventricular recovery after 15 mins of untreated cardiac arrest in pigs resuscitated with four 20-sec pauses during the first 3 mins of SNPeCPR combined with adenosine.

REFERENCES


