Pulmonary Vasodilator Therapy in Shock-associated Cardiac Arrest

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Abstract

Rationale: Many in-hospital cardiac arrests are precipitated by hypotension, often associated with systemic inflammation. These patients are less likely to be successfully resuscitated, and novel approaches to their treatment are needed.

Objectives: To determine if the addition of inhaled nitric oxide (iNO) to hemodynamic-directed cardiopulmonary resuscitation (HD-CPR) would improve short-term survival from cardiac arrest associated with shock and systemic inflammation.

Methods: In 3-month-old swine ($n = 21$), LPS was intravenously infused, inducing systemic hypotension. Ventricular fibrillation was induced, and animals were randomized to blinded treatment with either: 1) HD-CPR with iNO, or 2) HD-CPR without iNO. During HD-CPR, chest compression depth was titrated to peak aortic compression pressure of 100 mm Hg, and vasopressor administration was titrated to coronary perfusion pressure greater than or equal to 20 mm Hg. Defibrillation attempts began after 10 minutes of resuscitation. The primary outcome was 45-minute survival.

Measurements and Main Results: The iNO group had higher rates of 45-minute survival (10 of 10 vs. 3 of 11; $P = 0.001$). During cardiopulmonary resuscitation, the iNO group had lower pulmonary artery relaxation pressure (mean $\pm$ SEM, 10.9 ± 2.4 vs. 18.4 ± 2.4 mm Hg; $P = 0.03$), higher coronary perfusion pressure

(21.1 ± 1.5 vs. 16.9 ± 1.0 mm Hg; $P = 0.005$), and higher aortic relaxation pressure (36.6 ± 1.6 vs. 30.4 ± 1.1 mm Hg; $P < 0.001$) despite shallower chest compressions (5.88 ± 0.25 vs. 6.46 ± 0.40 cm; $P = 0.02$) and fewer vasopressor doses in the first 10 minutes (median, 4 [interquartile range, 3–4] vs. 5 [interquartile range, 5–6], $P = 0.03$).

Conclusions: The addition of iNO to HD-CPR in LPS-induced shock-associated cardiac arrest improved short-term survival and intraarrest hemodynamics.

Keywords: heart arrest; cardiopulmonary resuscitation; shock; inhaled nitric oxide

At a Glance Commentary

Scientific Knowledge on the Subject: Many in-hospital cardiac arrests are caused by hypotension and progressive shock, often in the setting of systemic inflammation. These patients are less likely to survive, and novel resuscitation approaches are needed.

What This Study Adds to the Field: The addition of inhaled nitric oxide to hemodynamic-directed cardiopulmonary resuscitation improves short-term survival and intraarrest hemodynamics in a porcine model of cardiac arrest preceded by hypotension and systemic inflammation.

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More than 200,000 patients have an in-hospital cardiac arrest annually in the United States (1). Hypotension is a precipitating factor for more than 60% of in-hospital cardiac arrests (2, 3), and many of these patients have septic shock or other causes of systemic inflammation and shock (4, 5). Notably, patients with shock and systemic inflammation at the time of in-hospital cardiac arrest are less likely to attain return of spontaneous circulation (ROSC) or to survive to hospital discharge than patients with cardiac arrests of other etiologies (5, 6). Because the success of cardiopulmonary resuscitation (CPR) depends on attaining adequate coronary perfusion pressure (the difference between aortic pressure and right atrial pressure during the relaxation phase of chest compressions) (7) and the pathophysiology of cardiac arrest precipitated by shock and systemic inflammation may adversely affect coronary perfusion pressure during CPR (8), it is not surprising that these patients are less likely to survive. Investigations of alternative resuscitation techniques that target the detrimental physiology of shock states are therefore warranted.

To that end, our previous swine investigations in primary ventricular fibrillation and asphyxial cardiac arrest models have established that hemodynamic-directed CPR (HD-CPR) can improve outcomes compared with standard, depth-guided CPR (9–13). However, this HD-CPR approach has not been applied to circulatory shock-associated in-hospital cardiac arrest. Therefore, we sought to study this method of patient-centric, physiology-oriented CPR in a model of cardiac arrest preceded by LPS-induced shock and systemic inflammation. However, pilot studies (described below) revealed uniform mortality with low coronary perfusion pressure and high pulmonary artery pressure. Because right ventricular dysfunction and pulmonary hypertension are well established in shock (14–17), and because elevated pulmonary vascular resistance is reported during cardiac arrest (18–20), we evaluated inhaled nitric oxide (iNO) in addition to HD-CPR and hypothesized that this would improve rates of short-term survival. Some of the preliminary results of this study have been previously reported in the form of an abstract (21).

Methods

Animal Preparation and Data Acquisition and Measurement

The Children's Hospital of Philadelphia Institutional Animal Care and Use Committee approved the experimental protocol, which is in concordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Comprehensive descriptions of animal preparation, anesthetic, and surgical methods are available in our previous publications (9–13, 22). Briefly, 3-month-old swine were anesthetized and mechanically ventilated. Vascular catheters were placed in the right atrium, pulmonary artery, and aorta for continuous hemodynamic measurements. Two unipolar pacing needles were inserted transcutaneously into the right ventricle for induction of ventricular fibrillation. Before and during the experimental protocol, the ECG, aortic blood pressure, right atrial pressure, pulmonary artery pressure, thermodilution-determined cardiac output, pulse oximetry, and end-tidal carbon dioxide were displayed and recorded. Coronary perfusion pressure was automatically calculated and displayed in real time by subtracting the right atrial pressure from the aortic pressure during the relaxation phase of chest compressions (10). Pulmonary capillary wedge pressure was measured at set time points throughout the experiment. Pulmonary artery pressure during CPR was measured during the relaxation phase of chest compressions to reflect pulmonary vascular resistance rather than the intrathoracic pressure generated during the compression phase. A CPR quality-recording defibrillator (Zoll R Series Plus; Zoll Medical Corporation) was used during CPR and recorded chest compression rate (per minute) and depth (centimeters).

Experimental Protocol

LPS-induced shock. Animals received LPS (*Escherichia coli* 055:B5; Sigma) via intravenous infusion (Figure 1). On the basis of work by others (23), the initial rate of the infusion was 7 $\mu\text{g/kg/h}$ and was increased stepwise (7, 14, and 20 $\mu\text{g/kg/h}$) every 10 minutes to a maximum rate of 20 $\mu\text{g/kg/h}$. In six pilot experiments, the infusion was continued for up to 2 hours

and the physiologic response was monitored. By 45 minutes into the LPS infusion, all animals had mean aortic pressure less than 75% of baseline and heart rate greater than 150% of baseline. As such, in the final experimental protocol, LPS was administered for a total of 45 minutes to ensure consistency in the cumulative LPS exposure before cardiac arrest. After 45 minutes, LPS was discontinued and ventricular fibrillation was electrically induced, at which time CPR was provided for 10 minutes before an initial defibrillation attempt. This ensured a consistent, minimum duration of CPR in which to study the treatment interventions and is clinically relevant because the median duration of in-hospital cardiac arrest is greater than 10 minutes (24).

Pilot studies and the rationale for pulmonary vasodilator therapy. We initially attempted to resuscitate three swine in pilot experiments with our previously described HD-CPR regimen after the LPS infusion. Despite near-universal short-term survival with this method of HD-CPR in other cardiac arrest models without preceding shock and inflammation (9, 10, 12), none of the animals in these pilot experiments attained the intraarrest hemodynamic goals or ROSC. We noted that the mean pulmonary artery pressure and pulmonary vascular resistance were increased before and during CPR in all of these pilot experiments. Therefore, we attempted to attenuate pulmonary vascular resistance with the provision of 80 ppm of iNO, a potent pulmonary vasodilator, to three additional animals. With the same LPS exposure and HD-CPR resuscitation method, all three pilot animals treated with iNO (open-label) attained intraarrest coronary perfusion pressure goals and 45-minute post-ROSC survival. We therefore designed a randomized, blinded investigation of iNO therapy in this model, in which swine were anesthetized, instrumented, and infused with LPS as described above.

Resuscitation period. In all swine, after confirmation of ventricular fibrillation, CPR commenced immediately with manual chest compressions (100/min, metronome-guided) and invasive mechanical ventilations (VT, 8 ml/kg; positive end-expiratory pressure, 5 mm Hg; rate, 10/min with 100% inhaled oxygen). All animals were provided with HD-CPR as

Figure 1. Experimental protocol. CoPP = coronary perfusion pressure; CPR = cardiopulmonary resuscitation; HD-CPR = hemodynamic-directed cardiopulmonary resuscitation; iNO = inhaled nitric oxide; ppm = parts per million; ROSC = return of spontaneous circulation; VF = ventricular fibrillation.

previously described (9, 11, 12). Chest compression depth was actively guided by the aortic blood pressure waveform with the intent to maintain a peak aortic compression pressure of 100 mm Hg. Vasopressors (epinephrine and vasopressin) were titrated according to aortic and right atrial pressure waveforms, with the intent to maintain a coronary perfusion pressure of at least 20 mm Hg. Animals were randomized to either receive iNO at 80 ppm or no iNO, and the study team was blinded to treatment group assignment during both the experiment and analysis.

The INOmax delivery system (Mallinckrodt Pharmaceuticals) was connected to the ventilator for all animals and the display screen was concealed so that only a single, unblinded study team member knew if iNO was provided. Beginning 1 minute into CPR, that individual provided either iNO at 80 ppm or no iNO and was not otherwise involved in the experimental protocol. The remainder of the team was blinded to treatment group assignment through the completion of all experiments. In both groups, after 10 minutes of CPR, an initial 200-Joule defibrillation attempt was provided. Resuscitation according to treatment group continued, with defibrillation attempts up to every 2 minutes until sustained ROSC was achieved or until an additional 10 minutes of CPR after the initial defibrillation attempt failed to result in ROSC. In animals attaining ROSC,

protocolized postarrest care was provided with active titration of anesthesia, mechanical ventilation and oxygenation, and intravenous epinephrine (infusion and bolus dosing), as necessary, to maintain mean arterial pressure greater than 55 mm

Hg. Animals in the iNO group continued to receive 80 ppm of iNO in a blinded manner through the duration of the postarrest period. Forty-five minutes after ROSC, surviving animals were humanely killed with potassium chloride after provision of

Figure 2. Study flowchart. HD-CPR = hemodynamic-directed cardiopulmonary resuscitation; iNO = inhaled nitric oxide.

Table 1. Prearrest Characteristics

	HD-CPR with iNO (n = 10)	HD-CPR (n = 11)	P Value
Baseline			
Heart rate, bpm	111.4 (5.4)	119.2 (6.9)	0.39
Aortic systolic pressure, mm Hg	100.6 (3.3)	101.7 (4.5)	0.85
Aortic diastolic pressure, mm Hg	70.0 (2.8)	73.5 (4.0)	0.49
Mean aortic pressure, mm Hg	80.3 (2.6)	83.0 (4.0)	0.59
Mean RA pressure, mm Hg	12.6 (0.9)	12.9 (0.8)	0.81
Mean PA pressure, mm Hg	21.7 (1.9)	22.0 (2.7)	0.93
End-tidal carbon dioxide, mm Hg	43.4 (42.3–44.6)	43.1 (41.5–44.8)	0.94
Cardiac output, L/min	3.3 (0.2)	3.1 (0.2)	0.49
LPS infusion—final 10 min			
Heart rate, bpm	129.1 (6.7)	135.8 (6.7)	0.43
Aortic systolic pressure, mm Hg	85.4 (4.0)	80.6 (3.8)	0.40
Aortic diastolic pressure, mm Hg	59.8 (2.8)	57.8 (4.0)	0.69
Mean aortic pressure, mm Hg	68.0 (3.1)	65.2 (3.0)	0.52
Mean RA pressure, mm Hg	13.4 (0.8)	12.4 (1.1)	0.48
Mean PA pressure, mm Hg	32.8 (2.7)	35.2 (3.8)	0.62
End-tidal carbon dioxide, mm Hg	43.3 (0.4)	42.6 (0.4)	0.24
Cardiac output, L/min	2.9 (0.2)	2.7 (0.2)	0.49

Definition of abbreviations: bpm = beats per minute; HD-CPR = hemodynamic-directed cardiopulmonary resuscitation; iNO = inhaled nitric oxide; PA = pulmonary artery; RA = right atrium.

Comparison between groups at baseline (mean values during 2 min preceding start of LPS infusion) and during final 10 minutes of LPS infusion, before cardiac arrest and randomization to treatment group. Values are means (SEM) or median (interquartile range). Comparisons performed using paired *t* test for normally distributed data, Wilcoxon rank-sum test for nonnormally distributed data.

high-dose isoflurane. Necropsies were performed on all animals to assess for injuries that may have contributed to outcome.

Outcomes and Statistical Analysis

The primary outcome was 45-minute postarrest survival. Secondary outcomes included 1) ROSC, 2) hemodynamics, 3) chest compression depth (centimeters), and 4) number of vasopressor doses. Continuous waveform data were recorded in PowerLab (ADInstruments, Colorado Springs, CO) and converted to numerical data, which were then summarized into 15-second data epochs using a custom code (MATLAB; MathWorks, Inc.). Dichotomous variables (e.g., survival outcomes) were compared using Fisher exact test. Normality of continuous variables was assessed with the skewness-kurtosis test. Normally distributed continuous variables were described as mean $\pm$ SEM and compared at predetermined times in the experimental protocol (baseline, during the LPS infusion, during CPR, post-ROSC) by Student's *t* test. Nonnormally distributed continuous variables were described as median with interquartile ranges (IQRs) and compared at these times using Wilcoxon rank-sum tests. Normally distributed paired data were compared using paired *t* tests.

Hemodynamic variables during CPR were compared using a generalized estimating equation regression model beginning 1 minute into CPR with the initiation of iNO or placebo, accounting for clustering of CPR epochs within individual animals. Twenty evaluable animals were planned in each group to allow 75% power to detect a 40% absolute difference (60% vs. 20%) in 45-minute survival. On the basis of pilot experiments, prerandomization animal attrition was estimated to be 20%, so 48 animal experiments were planned with an Institutional Animal Care and Use Committee–mandated interim analysis

after 24 total animals. Because of a statistically significant difference in the primary outcome between groups at the time of the interim analysis, the study was halted to decrease animal numbers (Figure 2). Statistical analyses were performed with the Stata IC statistical package (StataCorp).

Results

Twenty-one animals were randomized to HD-CPR with iNO or HD-CPR without iNO (Figure 2). At baseline and during the LPS infusion, there were no

Table 2. Hemodynamics during LPS Infusion

	Baseline	During LPS Infusion	P Value
Heart rate, bpm	115.6 (5.3)	168.9 (6.6)*	<0.001
Aortic systolic pressure, mm Hg	101.2 (2.5)	77.6 (2.3) [†]	<0.001
Aortic diastolic pressure, mm Hg	71.9 (2.3)	53.4 (1.6) [†]	<0.001
Mean aortic pressure, mm Hg	81.7 (2.3)	61.4 (1.8) [†]	<0.001
Mean RA pressure, mm Hg	12.8 (0.7)	12.6 (0.6) [‡]	0.88
Mean PA pressure, mm Hg	21.8 (1.6)	37.5 (2.1)*	<0.001

Definition of abbreviations: bpm = beats per minute; PA = pulmonary artery; RA = right atrium.

Comparison in all animals (n = 21) between baseline (mean values during 2 min preceding start of LPS infusion) and a 15-second data epoch during LPS infusion. Values are means (SEM). Comparisons performed using paired *t* test; all data were normally distributed.

*Peak values during LPS infusion.

[†]Lowest aortic blood pressure values during LPS infusion.

[‡]Value from final 15-second epoch of LPS infusion.

Table 3. Rates of Survival across Treatment Groups

	HD-CPR with iNO (n = 10)	HD-CPR (n = 11)	P Value
Any ROSC	10 (100)	4 (36)	0.004
45-min post-ROSC survival	10 (100)	3 (27)	0.001

Definition of abbreviations: HD-CPR = hemodynamic-directed cardiopulmonary resuscitation; iNO = inhaled nitric oxide; ROSC = return of spontaneous circulation. Comparisons between groups performed with Fisher exact test. Data are presented as n (%).

differences between treatment groups (Table 1). During the LPS infusion, all animals exhibited circulatory shock with tachycardia and systolic and diastolic systemic hypotension as well as increased pulmonary artery pressure and pulmonary vascular resistance compared with baseline (Table 2).

The iNO group was more likely to achieve ROSC (10 of 10 vs. 4 of 11 [36%]; $P = 0.004$) and to attain 45-minute post-ROSC survival (10 of 10 vs. 3 of 11 [27%]; $P = 0.001$) than those receiving HD-CPR alone (Table 3). During CPR, the iNO group had lower mean pulmonary artery relaxation pressure and had higher mean coronary perfusion pressure, aortic relaxation pressure, and peak aortic compression pressure (Table 4, Figure 3). Animals surviving to 45 minutes had higher mean coronary perfusion pressure during CPR than nonsurvivors (21.1 ± 1.3 vs. 15.3 ± 1.0 mm Hg; $P < 0.001$), with all survivors having mean coronary perfusion pressure values of at least 16 mm Hg.

Chest compression rates were not different between groups, whereas animals

treated with iNO required shallower chest compressions to achieve peak aortic compression pressure goals (Table 4). The number of vasopressors during CPR was lower in the iNO group in both the first 10 minutes of CPR (4 [IQR, 3, 4] vs. 5 [IQR, 5, 6], $P = 0.03$) and for the entire resuscitation period (4.5 [IQR, 4, 6] vs. 12 [IQR, 5, 13], $P = 0.03$). Among swine with ROSC, 8 of 10 animals treated with iNO and 4 of 4 treated without iNO required epinephrine infusions and/or boluses to maintain mean arterial pressures within goal. Systolic and diastolic aortic pressures and coronary perfusion pressure were higher in the iNO group during the postarrest period (Table 5). No animals had injuries identified on necropsy.

Discussion

This randomized, blinded, preclinical trial demonstrated that iNO during CPR increased rates of ROSC and short-term survival in a swine model of in-hospital cardiac arrest preceded by LPS-induced

circulatory dysfunction and systemic hypotension. The improved outcome with iNO during CPR is presumably through pulmonary vasodilation, as suggested by the lower pulmonary artery pressures during CPR and concomitant higher aortic relaxation pressures and coronary perfusion pressures.

In this study, systemic blood pressures and coronary perfusion pressure were substantially higher during CPR and during the postresuscitation period in the group treated with iNO. Because coronary perfusion pressure during CPR is directly correlated with myocardial blood flow (7, 25) and attaining coronary perfusion pressure greater than or equal to 20 mm Hg is associated with higher rates of ROSC and survival (7, 10–12, 22, 26, 27), the HD-CPR protocol targets a coronary perfusion pressure greater than or equal to 20 mm Hg. However, animals treated without iNO were typically unable to attain the target coronary perfusion pressure, and thus had a lower survival rate. Notably, the mean pulmonary artery relaxation pressure was lower in the iNO group, suggesting that iNO attenuated pulmonary vascular resistance during cardiac arrest and that the resultant increased transpulmonary flow led to more pulmonary venous return. In this HD-CPR model in which chest compression depth and vasopressor administration were titrated to hemodynamic response, the iNO group required shallower chest compressions and fewer doses of vasopressors, whereas the non-iNO group was unable to consistently attain hemodynamic goals despite these aggressive therapies (Figure 3). This suggests that in addition to the direct effects of increased transpulmonary blood flow on improving cardiac output during CPR, vasopressor delivery to the systemic circulation may have also been enhanced, with resultant increases in systemic vascular resistance, aortic pressure, and coronary perfusion pressure.

American Heart Association consensus guidelines recommend hemodynamic monitoring during CPR and maintenance of adequate coronary perfusion pressure (28, 29), but the methods for accomplishing this are unclear. HD-CPR is designed to address this, but optimization of chest compression quality and vasopressor administration alone cannot be expected to be effective in all patients. The addition of iNO to HD-CPR in groups of patients

Table 4. Measurements during Cardiopulmonary Resuscitation

	HD-CPR with iNO (n = 10)	HD-CPR (n = 11)	P Value
Coronary perfusion pressure, mm Hg	21.1 (1.5)	16.9 (1.0)	0.005
Aortic relaxation pressure, mm Hg	36.6 (1.6)	30.4 (1.1)	<0.001
Right atrial relaxation pressure, mm Hg	14.5 (0.9)	13.6 (0.6)	0.33
Pulmonary artery relaxation pressure, mm Hg	10.9 (2.4)	18.4 (2.4)	0.03
Peak aortic compression pressure, mm Hg	91.3 (4.4)	78.8 (3.1)	0.005
End-tidal carbon dioxide, mm Hg	23.8 (2.1)	22.8 (1.4)	0.62
Chest compression rate, per min	100.4 (0.4)	100.5 (0.7)	0.81
Chest compression depth, cm	5.88 (0.25)	6.46 (0.40)	0.02

Definition of abbreviations: HD-CPR = hemodynamic-directed cardiopulmonary resuscitation; iNO = inhaled nitric oxide.

Mean values from Minutes 1 to 10 of resuscitation period, compared using generalized estimating equation regression model. Parenthetical numbers indicate SEM. Relaxation pressures and coronary perfusion pressure measured during the release phase of chest compressions. Compression pressures indicate peak pressures during compression phase.

Figure 3. Coronary perfusion pressure during cardiopulmonary resuscitation. Coronary perfusion pressure during 10 minutes of cardiopulmonary resuscitation (CPR) in hemodynamic-directed (HD)-CPR with inhaled nitric oxide (iNO) versus HD-CPR without iNO. Error bars represent SEM. Comparison between groups using generalized estimating equation regression model.

suspected of having elevated pulmonary vascular resistance is a further step in physiologic goal-directed resuscitation. The findings of this study suggest that high pulmonary vascular resistance is a potential therapeutic target in a subset of patients. Further clinical investigations are necessary to elucidate the burden of reversible elevations in pulmonary vascular resistance among patients experiencing actual in-hospital cardiac arrest.

Most patients experiencing in-hospital cardiac arrest have shock or respiratory failure as the precipitant of cardiac arrest (4, 30, 31), and these disease states, along with cardiac arrest itself, are accompanied by hypoxemia and acidemia that increase

pulmonary vascular resistance (32, 33). Furthermore, epinephrine, the principal pharmacotherapeutic during CPR, can increase pulmonary vascular resistance (34). Among pulmonary vasodilators, iNO has a generally favorable safety profile (35–37); in particular, iNO induces less systemic vasodilation, an important issue during CPR because systemic vasodilation can decrease coronary perfusion pressure (38). Effective delivery of iNO to the pulmonary capillary bed may be limited in the setting of concomitant lung disease or by the relatively low minute ventilation provided during CPR. This study was performed with a high starting dose of iNO (80 ppm) to provide adequate NO to the

pulmonary vasculature, but future work is necessary for proper dose optimization.

Brücken and colleagues showed improved survival when iNO was administered during CPR in a rat model of ventricular fibrillation arrest (39). The same group demonstrated that pulmonary vascular resistance was elevated in a swine model of ventricular fibrillation cardiac arrest and that animals treated with iNO had lower pulmonary vascular resistance and higher coronary perfusion pressure than animals not treated with iNO. There was no survival benefit with iNO, but circulating markers of brain injury (S-100) and overall performance category values were superior in iNO-treated animals (40). Moreover, several investigators have evaluated the effects of iNO as a neuroprotective agent after successful resuscitation from cardiac arrest (41). NO directly scavenges reactive oxygen species and modulates mitochondrial dysfunction, potentially ameliorating ischemia–reperfusion injury after ROSC (42, 43). Both iNO and intravenous nitrites, which are converted to NO, have shown promise as neuroprotectants in preclinical studies (42, 44), but data in humans are limited to date (45).

This study has limitations. First, we examined short-term, 45-minute post-ROSC survival as the primary outcome in this trial. Future preclinical work with iNO during and after CPR should evaluate longer-term survival and assess for clinical neurologic recovery and differences in molecular and histologic markers of brain injury. Second, this model using LPS-driven hypotension and systemic inflammation differs from human in-hospital cardiac arrests precipitated by hypotension in the setting of systemic inflammation in terms of the time course, associated organ dysfunction, and overall clinical complexity (46). These differences could certainly impact iNO responsiveness if studied in human subjects and represent an important limitation regarding future research that could be drawn from the present results. This LPS model was used because it is reproducible and relatively uniform in terms of the injury severity, thus intending to improve the ability to assess a particular intervention while minimizing confounding variables. Third, we used a single, high dose (80 ppm) of iNO; further work is necessary to identify the optimal iNO dose for improving outcomes while

Table 5. Postarrest Measurements

	HD-CPR with iNO (n = 10)	HD-CPR (n = 4)	P Value
Heart rate, bpm	133.0 (11.6)	141.9 (9.9)	0.44
Coronary perfusion pressure, mm Hg	52.2 (4.5)	42.9 (3.8)	0.04
Aortic systolic pressure, mm Hg	95.1 (6.7)	81.3 (5.6)	0.04
Aortic diastolic pressure, mm Hg	65.7 (4.1)	56.5 (3.5)	0.03
Mean pulmonary artery pressure, mm Hg	25.7 (2.4)	26.6 (2.1)	0.72
End-tidal carbon dioxide, mm Hg	42.0 (1.5)	40.4 (1.3)	0.25
Cardiac output, L/min	2.6 (0.1)	2.7 (0.7)	0.96

Definition of abbreviations: bpm = beats per minute; HD-CPR = hemodynamic-directed cardiopulmonary resuscitation; iNO = inhaled nitric oxide.

Comparison between treatment groups among animals with return of spontaneous circulation during 45-minute postresuscitation period, compared using generalized estimating equation regression model. Parenthetical numbers indicate SEM.

limiting any potential toxicity. Fourth, it is possible that despite not causing any demonstrable CPR-related injuries, the deeper chest compressions provided to the HD-CPR group may have had deleterious hemodynamic effects. Fifth, although we hypothesize that iNO decreased pulmonary vascular resistance and improved pulmonary blood flow, we did not directly measure these hemodynamic variables or pulmonary mechanics during CPR. However, the combination of lower pulmonary artery

pressures and higher aortic pressures strongly suggests that pulmonary blood flow was increased.

Conclusions

In a porcine model of LPS-induced shock-associated cardiac arrest, iNO improved intraarrest hemodynamics and short-term survival. This study suggests that pulmonary vasodilator therapy has the potential to be a valuable component of hemodynamic-directed CPR in critically ill

patients suffering a cardiac arrest precipitated by hypotension and systemic inflammation. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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