ORIGINAL RESEARCH

# Effects of Different Doses of Pralidoxime Administered During Cardiopulmonary Resuscitation and the Role of α-Adrenergic Receptors in Its Pressor Action

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***Background***—We previously reported that pralidoxime facilitated restoration of spontaneous circulation by potentiating the pressor effect of epinephrine. We determined the optimal dose of pralidoxime during cardiopulmonary resuscitation and evaluated the involvement of α-adrenoceptors in its pressor action.

***Methods and Results***—Forty-four pigs randomly received 1 of 3 doses of pralidoxime (40, 80, or 120 mg/kg) or saline placebo during cardiopulmonary resuscitation, including epinephrine administration. Pralidoxime at 40 mg/kg produced the highest coronary perfusion pressure, whereas 120 mg/kg of pralidoxime produced the lowest coronary perfusion pressure. Restoration of spontaneous circulation was attained in 4 (36.4%), 11 (100%), 9 (81.8%), and 3 (27.3%) animals in the saline, 40, 80, and 120 mg/kg groups, respectively ($P<0.001$). In 49 rats, arterial pressure response to 40 mg/kg of pralidoxime was determined after saline, guanethidine, phenoxybenzamine, or phentolamine pretreatment, and the response to 200 mg/kg pf pralidoxime was determined after saline, propranolol, or phentolamine pretreatment. Pralidoxime at 40 mg/kg elicited a pressor response. Phenoxybenzamine completely inhibited the pressor response, but guanethidine and phentolamine did not. The pressor response of pralidoxime was even greater after guanethidine or phentolamine pretreatment. Pralidoxime at 200 mg/kg produced an initial vasodepressor response followed by a delayed pressor response. Unlike propranolol, phentolamine eliminated the initial vasodepressor response.

***Conclusions***—Pralidoxime at 40 mg/kg administered with epinephrine improved restoration of spontaneous circulation rate by increasing coronary perfusion pressure in a pig model of cardiac arrest, whereas 120 mg/kg did not improve coronary perfusion pressure or restoration of spontaneous circulation rate. The pressor effect of pralidoxime was unrelated to α-adrenoceptors and buffered by its vasodepressor action mediated by sympathoinhibition. **(*J Am Heart Assoc*. 2020;9:e015076. DOI: 10.1161/JAHA.119.015076.)**

**Key Words:** blood pressure • cardiopulmonary resuscitation • heart arrest • hemodynamics

Coronary perfusion pressure (CPP) is a major determinant of myocardial blood flow generated during cardiopulmonary resuscitation (CPR).[1] Higher CPP has consistently been associated with successful resuscitation in a number of experimental and clinical studies.[2–4] Hence, achieving adequate CPP during CPR is critical for successful resuscitation. Epinephrine has been used in the treatment of cardiac arrest for decades to improve CPP during CPR and increase the chances of restoration of spontaneous circulation (ROSC). It remains the mainstay medication for cardiac arrest. Human clinical trials have clearly shown increased rates of ROSC and survival to hospital admission with the administration of epinephrine, but the majority of patients with cardiac arrest still neither achieve ROSC nor are the majority admitted alive to hospital despite the administration of epinephrine.[5,6] Moreover, a recent large randomized trial of epinephrine in out-of-hospital cardiac arrest found that the increased rate of ROSC with the administration of epinephrine did not translate

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Received November 1, 2019; accepted January 29, 2020.

## Clinical Perspective

### What Is New?

- Pralidoxime facilitated restoration of spontaneous circulation after cardiac arrest by improving coronary perfusion pressure in a pig model.
- High-dose pralidoxime paradoxically exhibited vasodepressor action.
- Our findings suggest that the pressor effect of pralidoxime is unrelated to α-adrenoceptors and that this pressor effect is buffered by its vasodepressor action, mediated by inhibition of the sympathetic nervous system.

### What Are the Clinical Implications?

- Pralidoxime has the potential to improve survival after cardiac arrest.

into an increased rate of survival to hospital discharge with favorable neurological outcome.[6] Such findings warrant a need for new therapeutic options to improve survival after cardiac arrest.

Patients undergoing prolonged CPR typically receive epinephrine in repeated bolus doses. Multiple studies have reported that only the first of these repeated doses can increase CPP above a level that is needed for successful resuscitation, and that subsequent doses lose their effect and thus fail to improve CPP to a degree that increases the chance of achieving ROSC.[7–9] Pralidoxime is a cholinesterase reactivator that has been widely used as an antidote for organophosphate poisoning. Although its pressor effect as well as its potentiation of pressor effect of catecholamines have previously been reported,[10–13] this drug has not been used clinically as a vasopressor or an adjuvant drug to potentiate the pressor effect of catecholamines. We previously reported that 80 mg/kg of pralidoxime potentiated the vasopressor effect of epinephrine administered during CPR, particularly that of repeated doses.[14] Recently, we also demonstrated that the same dose of pralidoxime, in combination with epinephrine, significantly increased the rates of ROSC and short-term survival by improving CPP in a pig model of cardiac arrest.[15] However, many aspects of this therapy need to be studied further. First of all, the optimal dose of pralidoxime to be used during CPR is still not defined. A previous study in anesthetized dogs reported that pralidoxime increased arterial pressure in a dose-dependent manner.[12] Thus, it can be postulated that increasing the dose of pralidoxime can further improve CPP and rate of ROSC. However, dose-response effects of pralidoxime have not been studied in a cardiac arrest model. In addition, mechanisms underlying the pressor effect of pralidoxime remain controversial. Several studies reported that the pressor effect of pralidoxime was blocked by α-adrenergic blockers, including phenoxybenzamine and phentolamine,[10,11] suggesting that its pressor effect is mediated through stimulation of α-adrenergic receptors. However, the pressor effect of pralidoxime was not blocked by phentolamine in a study using isolated aortic strip preparation.[13]

In the present study, we investigated the effects of different doses of pralidoxime on CPP, rate of ROSC, and short-term survival rate in a pig model of cardiac arrest in order to determine the optimal dose of pralidoxime to be used during CPR. We also studied the effects of adrenergic antagonists on the pressor action of pralidoxime in anesthetized normal rats in an attempt to evaluate the possible involvement of the sympathetic nervous system in the pressor action of pralidoxime. We hypothesized that a higher dose of pralidoxime results in higher CPP, a higher rate of ROSC, and a higher rate of short-term survival. We also hypothesized that the pressor effect of pralidoxime is mediated through stimulation of α-adrenergic receptors.

## Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. The present study consisted of 2 substudies. The first substudy investigated the effects of different doses of pralidoxime in 44 Yorkshire/Landrace cross pigs (23.2±3.5 kg) that underwent ventricular fibrillation (VF) cardiac arrest with subsequent CPR and was approved by the Animal Care and Use Committee of Chonnam National University (CNU IACUC-H-2018-26). The second substudy investigated the effects of adrenergic antagonists on the pressor action of pralidoxime in 61 anesthetized normal Wistar rats (302±5 g) and was approved by the Animal Care and Use Committee of Chonnam National University Hospital (CNUH IACUC-18002). All animal care was compliant with Institutional Animal Care and Use Committee guidelines.

### Study to Investigate the Effects of Different Doses of Pralidoxime Administered During CPR

Anesthesia, animal preparation, and data-recording procedures used in this study have been described previously.[14,15] Following initial sedation with intramuscular ketamine (20 mg/kg) and xylazine (2.2 mg/kg), inhaled sevoflurane (0.5–2.0%) was used for anesthesia during animal preparation procedures. After endotracheal intubation, pigs were ventilated with an oxygen/nitrous oxide mixture (3:7) using an anesthesia machine, with a tidal volume of 10 mL/kg and a respiratory rate adjusted to maintain normocapnia. A 7.0-F double-lumen catheter was advanced through the right

femoral artery into the descending aorta for aortic pressure monitoring and blood sampling, and a 5.0-F thermistor-tipped catheter (VolumeView femoral arterial catheter; Edwards Lifesciences, Irvine, CA) was placed in the left femoral artery for hemodynamic measurements using a transpulmonary thermodilution technique. A 6.0-F introducer sheath was advanced through the right external jugular vein to monitor right atrial pressure and to insert a right ventricle pacing catheter. For echocardiographic measurements, a transesophageal echocardiography probe (UST-5293-5; Hitachi Aloka Medical Ltd., Tokyo, Japan) was inserted precordially through a subcutaneous pocket created just below the xiphoid process, as described previously.[14–17] Animals' rectal temperature was maintained at 37.5±0.5°C during the preparation period.

Immediately before inducing VF, animals were randomly assigned by sealed envelope to 1 of 4 pralidoxime dose groups: pralidoxime-40 group (40 mg/kg), pralidoxime-80 group (80 mg/kg), pralidoxime-120 group (120 mg/kg), and a control group (saline placebo). The investigator opening the envelope prepared the prescribed drug in equal volumes (20 mL). All other investigators remained blinded to group assignment during experiments. VF was induced by applying an electrical current (60 Hz and 30 mA alternating current) through a temporary pacing wire positioned in the right ventricle. After 15 minutes of untreated VF (Figure 1), closed-chest CPR was started using a mechanical chest compression device (Life-Stat; Michigan Instruments, Grand Rapids, MI). Chest compressions were delivered at a rate of 100 compressions per minute, with a 50% duty cycle and a compression depth comparable to 20% of the anterior-posterior chest diameter. During CPR, positive-pressure ventilations with high-flow oxygen (15 L/min) were delivered at a rate of 10 breaths per minute using a volume-marked manual resuscitator bag.[18] Coincident with the start of chest compressions, either 40 (pralidoxime-40 group), 80 (pralidoxime-80 group), or 120 mg/kg (pralidoxime-120 group) of pralidoxime chloride or a saline placebo (control group) was administered into the right atrium. During CPR, animals received 0.02 mg/kg of epinephrine every 3 minutes. Electrical defibrillation with a single biphasic 150-J shock was delivered every 2 minutes, if indicated. Sustained ROSC was defined as an organized cardiac rhythm with a systolic aortic pressure >60 mm Hg for at least 10 minutes.[19] CPR was continued until ROSC was achieved or for a total of 14 minutes.

Animals that achieved ROSC underwent intensive care for 6 hours under general anesthesia with sevoflurane. Immediately following ROSC, animals received positive pressure ventilation with 100% oxygen at prearrest setting, and oxygen concentration was reduced to 40% at 5 minutes after ROSC. One liter of normal saline at room temperature was given intravenously throughout the 6-hour period. Animals with hypotension received norepinephrine infusion, which was titrated to maintain a mean arterial pressure >65 mm Hg. After finishing the experimental protocol, animals were euthanized with an overdose of potassium chloride under general anesthesia. Autopsy was routinely performed for documentation of organ injuries related to CPR.

Primary outcomes were CPP during CPR and ROSC. Aortic pressure and right atrial pressure were recorded continuously. CPP was calculated from the difference between aortic end-diastolic pressure and right atrial end-diastolic pressure. Left ventricular ejection fraction was assessed by using Simpson's method at the prearrest baseline and at 30 minutes and 6 hours after ROSC. Cardiac index, stroke volume index, global end-diastolic volume index, global ejection fraction, and systemic vascular resistance index were measured by using transpulmonary thermodilution technique (VolumeView; Edwards Lifesciences) at the prearrest baseline and at 30 minutes, 1 hour, 3 hours, and 6 hours after ROSC. Arterial blood gases (RapidLab865; Bayer Health Care, Fernwald, Germany), lactate (Unicel DXC 800; Beckman Coulter, Fullerton, CA), aspartate aminotransferase, alanine aminotransferase, creatinine, and troponin-I (Dimension RXL Max; Siemens Healthcare Diagnostics, Deerfield, IL) were measured at prearrest baseline and at 6 hours after ROSC.

## Study to Investigate the Effects of Adrenergic Antagonists on the Pressor Action of Pralidoxime

After intubation following anesthesia with isoflurane (5%), rats were mechanically ventilated with a tidal volume of 6 mL/kg and a respiratory rate adjusted to maintain normocapnia. During experiments, anesthesia was maintained using an oxygen/nitrous oxide mixture (3:7) and 1% to 2% isoflurane, and rectal temperature was maintained at 37.0±0.5°C. Twenty-four-gauge catheters were placed in the left femoral and right jugular veins for administration of pralidoxime and adrenergic antagonists, respectively, and in the right femoral artery for monitoring arterial pressure and heart rate.

Forty-nine rats were divided to 7 experimental groups (N=7 each). In the first 4 groups of experiments that were designed to determine involvement of α-adrenergic receptors in the pressor effect of pralidoxime, guanethidine monosulfate (6 mg/kg), phenoxybenzamine hydrochloride (9 mg/kg), phentolamine mesylate (9 mg/kg), or 0.9% saline (1 mL) was administered intravenously following a stabilization period of at least 30 minutes. All adrenergic antagonists were purchased from the US Pharmacopeial Convention (Rockville, IL) and dissolved in 1 mL of 0.9% saline. To allow antagonists to fully develop their α-adrenergic–blocking effects, 15 minutes were allowed to elapse after the administration of guanethidine, phentolamine, or saline, whereas 60 minutes were

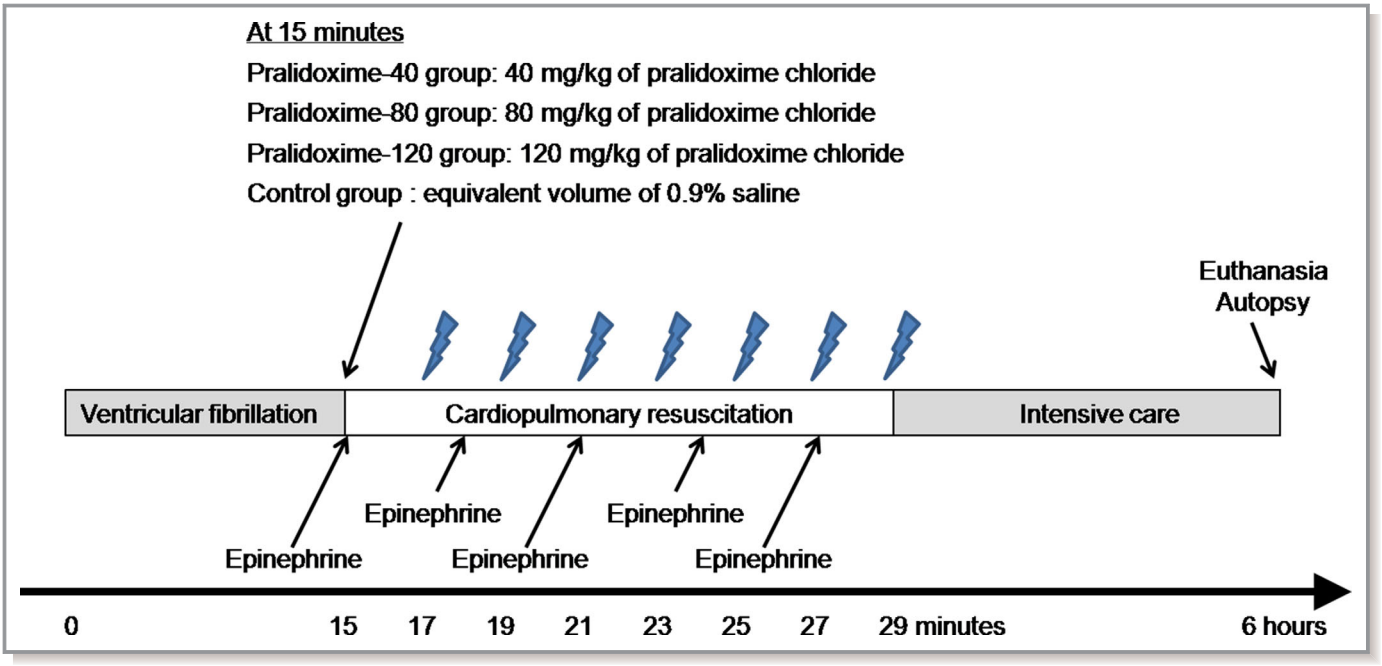


**Figure 1.** Experimental timeline. At 15 minutes after induction of ventricular fibrillation, either 40 (pralidoxime-40 group), 80 (pralidoxime-80 group), or 120 mg/kg (pralidoxime-120 group) of pralidoxime chloride or an equivalent volume of 0.9% saline solution (control group) was administered into the right atrium. Lightning marks indicate onset of a 10-second pause in chest compressions for rhythm analysis and a 150-J shock, if indicated.

allowed to elapse after the administration of phenoxybenzamine. At this point, 40 mg/kg of pralidoxime chloride was administered intravenously, and changes in diastolic arterial pressure (an indicator of systemic vascular resistance) produced by the pralidoxime administration were recorded every minute for 10 minutes. In the first substudy, which was conducted on pigs undergoing CPR, 120 mg/kg of pralidoxime resulted in lower CPP than saline placebo, although the difference was not statistically significant. Accordingly, another 3 groups (N=7 each) of rats were added to the experimental design to determine whether pralidoxime, when administered in a high dose, paradoxically exhibits vasodepressor action and to characterize mechanisms responsible for the potential vasodepressor action. Pralidoxime chloride at 200 mg/kg was administered 15 minutes after intravenous administration of 0.9% saline (1 mL), phentolamine mesylate (9 mg/kg), or propranolol hydrochloride (9 m/kg), and changes in diastolic arterial pressure were recorded for 10 minutes. Moreover, 12 rats were used to assess the efficacy of α- and β-adrenergic blockade in the present study. Maximal arterial pressure responses to norepinephrine (1 μg/kg) were determined before and 15 minutes after administering phentolamine (9 mg/kg) to assess the efficacy of α-adrenergic blockade with phentolamine (N=6). Maximal arterial pressure responses to isoproterenol (2 μg/kg) were also determined before and 15 minutes after administering propranolol (9 mg/kg) to assess the efficacy of β-adrenergic blockade with propranolol (N=6).

## Statistical Analysis

Sample size of the first substudy was calculated based on the CPP data from a pilot study. We calculated a sample size of 8 animals in each group to reach an α of 0.05 and a power of 90%. To minimize any effect of data loss, 11 animals per group were included for the first substudy. Normally distributed continuous variables are expressed as mean±SD, whereas non-normally distributed continuous variables are expressed as medians with interquartile ranges, unless otherwise specified. Categorical variables are shown as numbers of cases with percentages. For the first substudy, 1-way ANOVA or the Kruskal–Wallis test was used to compare continuous variables among the 4 groups. Comparisons of categorical variables were performed using Fisher's exact test. We did not include aortic pressure and CPP data after ROSC in the comparisons of hemodynamic measurements during CPR. Thus, mixed-model analysis, which can retain cases with missing data points, was used for comparisons of serial hemodynamic measurements during CPR. Post hoc comparisons were made using 1-way ANOVA with Bonferroni's adjustment at given time points. For the second substudy, the Wilcoxon signed-ranks test was used to compare diastolic arterial pressure and heart rate before and after pretreatment within groups. Repeated-measures ANOVA, followed by pairwise comparison with Bonferroni's adjustment, was used for comparisons of serial hemodynamic measurements. Data were analyzed using SPSS for Windows (version 18.0; SPSS,

**Table 1.** Baseline Characteristics

| | Control Group (N=11) | Pralidoxime-40 Group (N=11) | Pralidoxime-80 Group (N=11) | Pralidoxime-120 Group (N=11) | *P* Value* |
|---|---|---|---|---|---|
| Systolic aortic pressure, mm Hg | 120±7 | 117±15 | 123±11 | 114±12 | 0.261 |
| Diastolic aortic pressure, mm Hg | 79±10 | 72±16 | 82±13 | 73±14 | 0.332 |
| Mean aortic pressure, mm Hg | 97±9 | 91±17 | 99±12 | 90±13 | 0.340 |
| Systolic right atrial pressure, mm Hg | 10 (9–11) | 10 (9–12) | 9 (9–11) | 9 (9–9) | 0.261 |
| Diastolic right atrial pressure, mm Hg | 6 (5–7) | 6 (5–7) | 6 (5–6) | 5 (4–6) | 0.237 |
| Mean right atrial pressure, mm Hg | 8 (8–9) | 8 (7–9) | 7 (7–9) | 7 (7–8) | 0.454 |
| Heart rate, beats/min | 97 (87–105) | 85 (74–93) | 100 (91–106) | 98 (88–115) | 0.065 |
| End-tidal carbon dioxide, mm Hg | 39 (38–42) | 40 (39–42) | 39 (36–41) | 38 (36–39) | 0.442 |
| pH | 7.491±0.052 | 7.504±0.057 | 7.490±0.034 | 7.496±0.031 | 0.880 |
| $PaCO_2$, mm Hg | 39.6 (36.6–40.3) | 37.8 (36.9–39.4) | 36.3 (35.5–40.3) | 38.8 (37.1–39.7) | 0.916 |
| $PaO_2$, mm Hg | 149.2±29.4 | 155.7±27.3 | 145.0±23.6 | 148.3±32.4 | 0.842 |
| Base excess, mmol/L | 5.5±2.6 | 6.4±3.6 | 5.4±2.5 | 5.8±2.2 | 0.858 |
| $HCO_3^-$, mmol/L | 28.8±2.4 | 29.5±3.1 | 28.8±2.4 | 29.1±2.0 | 0.901 |
| $SaO_2$ (%) | 99.7 (99.5–99.9) | 99.6 (99.4–99.7) | 99.3 (99.1–99.9) | 99.6 (99.4–99.8) | 0.691 |
| Troponin, ng/mL | 0.09 (0.03–0.10) | 0.05 (0.02–0.11) | 0.10 (0.05–0.15) | 0.05 (0.04–0.12) | 0.486 |
| Lactate, mmol/L | 0.79 (0.70–1.22) | 1.34 (0.98–1.67) | 1.46 (1.28–1.96) | 0.96 (0.86–1.34) | 0.137 |
| Aspartate aminotransferase, U/L | 24 (22–32) | 26 (21–37) | 23 (20–34) | 22 (19–30) | 0.634 |
| Alanine aminotransferase, U/L | 33±7 | 37±19 | 30±7 | 30±10 | 0.401 |
| Creatinine, mg/dL | 0.85±0.12 | 0.84±0.26 | 0.92±0.16 | 0.91±0.14 | 0.627 |
| Left ventricular ejection fraction (%) | 54.9 (53.0–56.5) | 59.0 (49.4–64.2) | 53.9 (47.5–57.7) | 62.2 (55.6–64.0) | 0.204 |
| Cardiac index, L/min/$m^{2\dagger}$ | 1.7 (1.6–1.9) | 1.6 (1.5–1.7) | 1.8 (1.5–2.0) | 1.9 (1.6–2.0) | 0.445 |
| Stroke volume index, mL/beat/$m^{2\dagger}$ | 19 (17–20) | 19 (16–22) | 17 (16–20) | 17 (16–18) | 0.645 |
| Global end-diastolic volume index, mL/$m^{2\dagger}$ | 271 (247–295) | 282 (277–352) | 281 (264–306) | 264 (251–282) | 0.263 |
| Extravascular lung water index, mL/kg$^\dagger$ | 11 (10–12) | 12 (11–14) | 11 (11–12) | 13 (12–14) | 0.273 |
| Global ejection fraction (%$^\dagger$ | 28 (27–29) | 26 (25–27) | 27 (25–30) | 27 (25–29) | 0.725 |
| Pulmonary vascular permeability index (%)$^\dagger$ | 2.5 (2.5–2.9) | 2.6 (2.5–2.8) | 2.5 (2.3–2.9) | 2.9 (2.6–3.5) | 0.302 |
| Systemic vascular resistance index, dyne·sec·$m^2$/$cm^{5\dagger}$ | 3814 (3507–4464) | 4342 (3685–4751) | 3686 (3241–4707) | 3789 (3326–4129) | 0.259 |

Data are presented as mean±SD or medians with interquartile ranges. $HCO_3^-$ indicates bicarbonate; $PaCO_2$ indicates partial pressure of carbon dioxide; $PaO_2$, partial pressure of oxygen; $SaO_2$, oxygen saturation.

**P* value by 1-way ANOVA or Kruskal–Wallis test.

†Data were obtained in 9, 10, and 10 animals in the pralidoxime-40, pralidoxime-80, and pralidoxime-120 groups, respectively.

Inc, Chicago, IL). A 2-tailed *P* value of <0.05 was considered statistically significant.

## Results

### Effects of Different Doses of Pralidoxime Administered During CPR

There were no significant differences among the 4 groups in baseline measurements (Table 1). Figure 2 shows systolic aortic pressure, diastolic aortic pressure, and CPP during CPR. As shown in Figure 2, pralidoxime-40 group animals exhibited the highest CPP values among the 4 groups, whereas pralidoxime-120 group animals had the lowest CPP values, particularly for 3 minutes after pralidoxime administration. Mixed-model analyses of systolic aortic pressure, diastolic aortic pressure, and CPP revealed significant group-time interactions (all *P*<0.001). In post hoc analyses, systolic aortic pressure, diastolic aortic pressure, and CPP were significantly higher in the pralidoxime-40 group than in the control group for 4 minutes after pralidoxime administration. These pressures were significantly lower in both the pralidoxime-80 and pralidoxime-120 groups than in the pralidoxime-40 group for 3 minutes after pralidoxime administration. Sustained ROSC was attained in 4 (36.4%), 11 (100%), 9 (81.8%), and 3 (27.3%) animals in the control, pralidoxime-40, pralidoxime-80, and

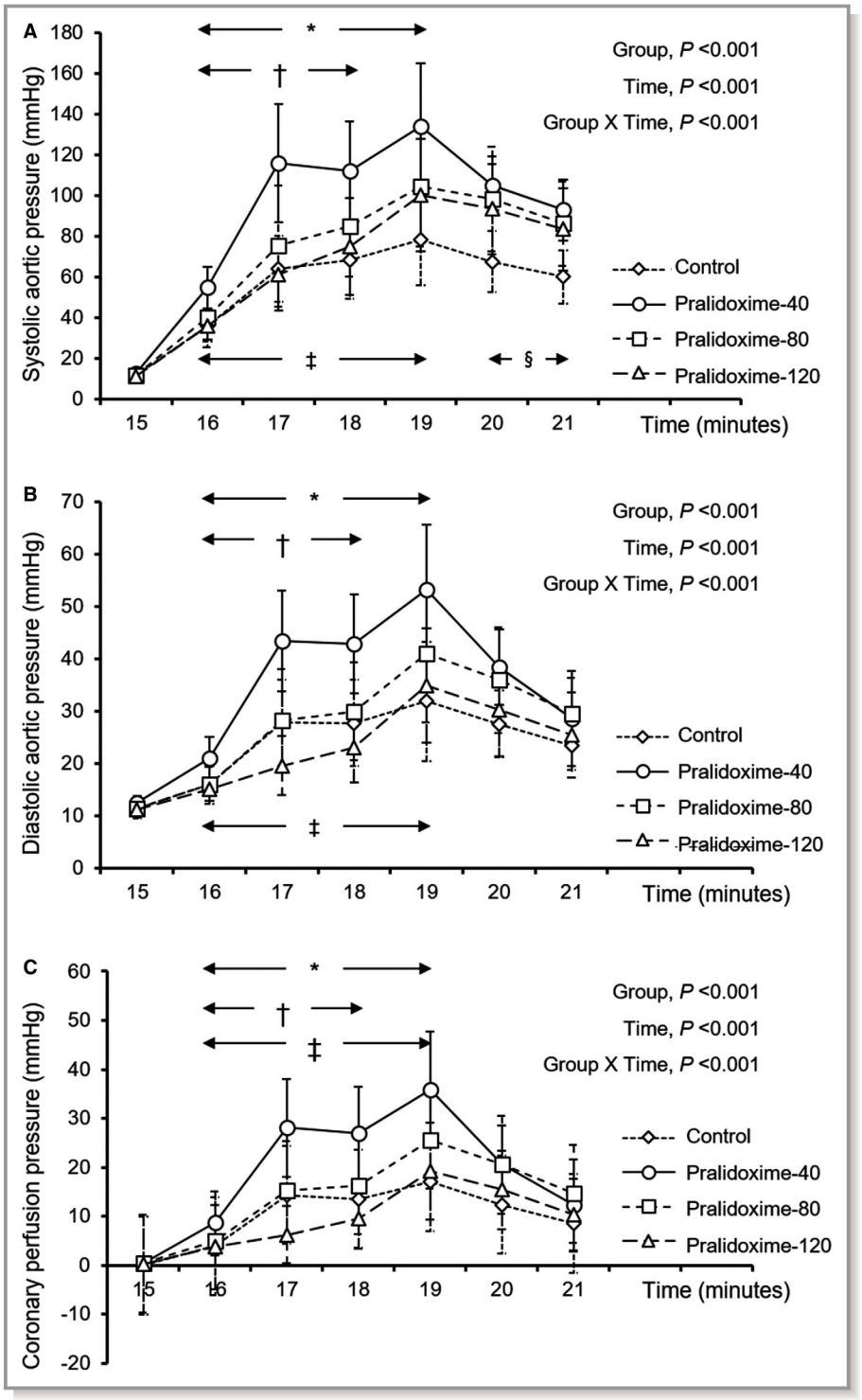


**Figure 2.** Systolic aortic pressure (**A**), diastolic aortic pressure (**B**), and coronary perfusion pressure (**C**) during cardiopulmonary resuscitation. Data are presented as mean±SD. Comparisons of these variables were made using data obtained within 21 minutes after induction of ventricular fibrillation, given that the number of animals still in cardiac arrest markedly decreased after 21 minutes in the pralidoxime groups. **P*<0.05 (control group vs pralidoxime-40 group); †*P*<0.05 (pralidoxime-40 group vs pralidoxime-80 group); ‡*P*<0.05 (pralidoxime-40 group vs pralidoxime-120 group); §*P*<0.05 (control group vs all the other groups).

**Table 2.** Resuscitation Outcomes

| | Control Group | Pralidoxime-40 Group | Pralidoxime-80 Group | Pralidoxime-120 Group | *P* Value* |
|---|---|---|---|---|---|
| Sustained ROSC | 4 (36.4) | 11 (100) | 9 (81.8) | 3 (27.3) | <0.001 |
| 6-h survival | 4 (36.4) | 11 (100) | 8 (72.7) | 3 (27.3) | 0.001 |

Data are presented as number (percentage). ROSC indicates restoration of spontaneous circulation.
**P* value by Fisher's exact test.

pralidoxime-120 groups, respectively ($P<0.001$; Table 2). Resuscitation variables in successfully resuscitated animals are shown in Table 3. Of the animals that achieved sustained ROSC, 1 animal in the pralidoxime 80 group died 30 minutes after ROSC because of severe cardiogenic shock refractory to norepinephrine infusion. Thus, 4 (36.4%), 11 (100%), 8 (72.7%), and 3 (27.3%) animals survived the 6-hour intensive care period in the control, pralidoxime-40, pralidoxime-80, and pralidoxime-120 groups, respectively ($P=0.001$). Hemodynamic and laboratory variables after ROSC are shown in Table 4 and Figure 3.

## Effects of Adrenergic Antagonists on the Pressor Action of Pralidoxime

Baseline values of diastolic arterial pressure and heart rate are shown in Table 5. Guanethidine and phentolamine markedly reduced diastolic arterial pressure and heart rate, while saline did not affect them. Phenoxybenzamine reduced diastolic arterial pressure but did not affect heart rate. Propranolol reduced heart rate, but did not affect diastolic arterial pressure. Phentolamine at the dose used in this study markedly attenuated arterial pressure responses produced by intravenous bolus injection of norepinephrine. Before administration of phentolamine, norepinephrine increased diastolic arterial pressure by 28 mm Hg (24–35), whereas after phentolamine administration, norepinephrine increased diastolic arterial pressure by 12 mm Hg (7–18; $P=0.016$). Vasodepressor responses produced by isoproterenol (−20 mm Hg [−26 to −18]) were essentially abolished by previous treatment with propranolol (2 mm Hg [0–3]; $P=0.004$).

Figure 4 shows the effects of these pretreatments on the pressor action of pralidoxime. After saline pretreatment, diastolic arterial pressure gradually increased following administration of 40 mg/kg of pralidoxime, reached a peak (increase in diastolic arterial pressure of 5.9±2.0 mm Hg) at 3 minutes after administration, and gradually decreased thereafter. Pretreatment with phenoxybenzamine completely inhibited the pressor effect of 40 mg/kg of pralidoxime (group effect, $P=0.007$; Figure 4B), but neither guanethidine (Figure 4A) nor phentolamine (Figure 4C) inhibited the pressor effect of pralidoxime. The increase in diastolic arterial pressure following pralidoxime administration was even greater after pretreatment with guanethidine (group effect, $P=0.037$) or with phentolamine (group-time interaction, $P=0.025$). In addition, both guanethidine and phentolamine pretreatments produced a transient sharp elevation in arterial pressure within the first minute after the administration of pralidoxime. Administration of 200 mg/kg of pralidoxime produced a biphasic arterial pressure response, which comprised an initial decrease in arterial pressure that lasted ≈3 minutes followed by a delayed increase in arterial pressure (group-time interaction, $P<0.001$ versus 40 mg/kg of pralidoxime after saline pretreatment; Figure 4D). Pretreatment with propranolol, which was included to determine whether the initial decrease in arterial pressure was caused by β-2 adrenergic receptor stimulation, did not abolish the initial decrease in arterial pressure (Figure 4E), but pretreatment with phentolamine abolished the initial vasodepressor response and even reversed it, causing a sharp increase in arterial pressure (group-time interaction, $P<0.001$ versus 200 mg/kg of pralidoxime after saline treatment; Figure 4F).

**Table 3.** Resuscitation Variables in Successfully Resuscitated Animals

| | Control Group (N=4) | Pralidoxime-40 Group (N=11) | Pralidoxime-80 Group (N=9) | Pralidoxime-120 Group (N=3) |
|---|---|---|---|---|
| No. of countershocks (no) | 4 (3–7) | 3 (2–6) | 4 (3–6) | 3, 8, 12 |
| No. of epinephrine administrations (no) | 3 (2–4) | 2 (2–3) | 3 (2–4) | 2, 4, 5 |
| Duration of ACLS, min | 7 (6–9) | 4 (4–7) | 8 (6–10) | 6, 10, 14 |

Data are presented as medians with interquartile ranges in control, pralidoxime-40, and pralidoxime-80 groups. ACLS indicates advanced cardiovascular life support.

**Table 4.** Hemodynamic and Laboratory Variables After Restoration of Spontaneous Circulation and Norepinephrine Requirements During the Intensive Care Period

| | Control Group (N=4) | Pralidoxime-40 Group (N=11) | Pralidoxime-80 Group (N=9)* | Pralidoxime-120 Group (N=3) |
|---|---|---|---|---|
| 30 min after ROSC | | | | |
| Systolic aortic pressure, mm Hg | 133 (130–140) | 150 (123–156) | 142 (133–148) | 138, 143, 172 |
| Diastolic aortic pressure, mm Hg | 104 (101–107) | 97 (82–114) | 100 (94–103) | 71, 99, 125 |
| Mean aortic pressure, mm Hg | 114 (111–118) | 120 (99–126) | 113 (111–119) | 92, 115, 140 |
| Systolic RA pressure, mm Hg | 13 (11–13) | 12 (11–14) | 9 (9–12) | 6, 14, 15 |
| Diastolic RA pressure, mm Hg | 9 (7–10) | 8 (7–9) | 6 (5–8) | 2, 5, 8 |
| Mean RA pressure, mm Hg | 10 (9–11) | 9 (9–10) | 7 (6–9) | 4, 8, 12 |
| Heart rate, beats/min | 154 (145–164) | 126 (119–149) | 153 (145–171) | 133, 171, 176 |
| LVEF (%) | 27.6 (21.3–34.1) | 39.0 (22.8–42.4) | 35.0 (31.3–49.2) | 31.9, 46.5, 49.3 |
| 1 h after ROSC | | | | |
| Systolic aortic pressure, mm Hg | 122 (116–127) | 107 (90–129) | 116 (112–123) | 100, 120, 130 |
| Diastolic aortic pressure, mm Hg | 95 (90–97) | 62 (55–87) | 85 (74–85) | 62, 73, 95 |
| Mean aortic pressure, mm Hg | 106 (100–109) | 85 (67–101) | 95 (90–99) | 78, 91, 107 |
| Systolic RA pressure, mm Hg | 11 (10–12) | 13 (11–15) | 13 (10–13) | 7, 12, 12 |
| Diastolic RA pressure, mm Hg | 7 (6–8) | 7 (5–10) | 7 (4–10) | 2, 4, 6 |
| Mean RA pressure, mm Hg | 8 (7–10) | 9 (8–12) | 9 (7–12) | 5, 6, 9 |
| Heart rate, beats/min | 131 (110–161) | 122 (96–139) | 143 (126–150) | 143, 147, 154 |
| 3 h after ROSC | | | | |
| Systolic aortic pressure, mm Hg | 129 (103–150) | 128 (111–147) | 118 (111–126) | 131, 132, 137 |
| Diastolic aortic pressure, mm Hg | 95 (75–112) | 90 (70–101) | 78 (73–87) | 91, 102, 103 |
| Mean aortic pressure, mm Hg | 107 (84–128) | 110 (88–119) | 94 (89–100) | 108, 113, 116 |
| Systolic RA pressure, mm Hg | 13 (9–16) | 11 (11–15) | 14 (12–15) | 9, 10, 13 |
| Diastolic RA pressure, mm Hg | 8 (5–10) | 7 (5–9) | 8 (5–9) | 3, 6, 8 |
| Mean RA pressure, mm Hg | 10 (7–13) | 9 (8–12) | 10 (8–11) | 5, 7, 10 |
| Heart rate, beats/min | 137 (127–142) | 135 (98–150) | 125 (111–154) | 136, 147, 151 |
| 6 h after ROSC | | | | |
| Systolic aortic pressure, mm Hg | 110 (104–121) | 110 (108–124) | 126 (115–130) | 121, 129, 144 |
| Diastolic aortic pressure, mm Hg | 73 (69–84) | 66 (65–77) | 78 (69–84) | 79, 81, 90 |
| Mean aortic pressure, mm Hg | 88 (84–100) | 87 (85–95) | 97 (88–101) | 98, 104, 106 |
| Systolic RA pressure, mm Hg | 14 (13–15) | 12 (10–14) | 13 (11–13) | 10, 14, 15 |
| Diastolic RA pressure, mm Hg | 9 (6–10) | 7 (6–9) | 7 (5–8) | 5, 7, 7 |
| Mean RA pressure, mm Hg | 12 (10–12) | 9 (9–11) | 9 (7–10) | 7, 9, 12 |
| Heart rate, beats/min | 103 (89–122) | 124 (106–145) | 128 (122–143) | 105, 125, 214 |
| pH | 7.476 (7.408–7.479) | 7.439 (7.392–7.453) | 7.418 (7.357–7.447) | 7.187, 7.430, 7.480 |
| $PaCO_2$, mm Hg | 38.0 (36.8–39.1) | 38.6 (36.8–41.1) | 41.2 (38.1–44.5) | 36.7, 41.2, 60.6 |
| $PaO_2$, mm Hg | 172.8 (166.7–177.5) | 167.0 (159.0–174.4) | 135.5 (119.1–156.4) | 109.0, 122.1, 136.5 |
| Base excess, mmol/L | 2.6 (−1.5 to 4.2) | 1.2 (−0.1 to 2.0) | 1.1 (−0.8 to 1.8) | −5, 2.4, 3.2 |
| $HCO_3^-$, mmol/L | 26.2 (22.8–27.7) | 25.2 (24.0–26.0) | 25.1 (24.0–25.6) | 22.1, 26.7, 26.7 |
| $S_aO_2$ (%) | 99.7 (99.5–99.8) | 100.0 (99.7–100.0) | 99.1 (97.4–99.7) | 97.2, 98.6, 99.5 |
| Troponin, ng/mL | 24.03 (15.73–33.13) | 11.03 (4.29–36.18) | 50.97 (26.64–96.19) | 8.22, 21.00, 103.08 |

Continued

**Table 4.** Continued

| | Control Group (N=4) | Pralidoxime-40 Group (N=11) | Pralidoxime-80 Group (N=9)* | Pralidoxime-120 Group (N=3) |
|---|---|---|---|---|
| Lactate, mmol/L | 1.02 (0.99–2.23) | 1.19 (0.81–1.83) | 2.68 (1.64–3.44) | 1.00, 1.60, 2.08 |
| Aspartate aminotransferase, U/L | 78 (64–101) | 78 (39–103) | 97 (85–164) | 36, 59, 108 |
| Alanine aminotransferase, U/L | 31 (29–35) | 32 (23–61) | 36 (30–39) | 21, 24, 24 |
| Creatinine, mg/dL | 0.97 (0.94–1.05) | 0.95 (0.78–1.01) | 1.17 (1.07–1.19) | 1.13, 1.44, 1.60 |
| LVEF (%) | 47.1 (34.3–56.2) | 38.4 (31.9–43.9) | 36.3 (32.4–45.8) | 37.2, 35.8, 43.8 |
| Norepinephrine requirements, mg | 0.06 (0–0.91) | 0 (0–0.11) | 0 (0–0) | 0, 0, 0.04 |

Data are presented as medians with interquartile ranges. $HCO_3^-$ indicates bicarbonate; LVEF, left ventricular ejection fraction; $PaCO_2$, partial pressure of carbon dioxide; $PaO_2$, partial pressure of oxygen; RA, right atrial; ROSC, restoration of spontaneous circulation; $SaO_2$, oxygen saturation.
*n=8 at 1, 3, and 6 hours after restoration of spontaneous circulation.

## Discussion

To our knowledge, this is the first study evaluating the effects of different doses of pralidoxime in an in vivo cardiac arrest model. We initially expected that high-dose pralidoxime would provide superior hemodynamics during CPR and improve resuscitation outcome compared with low-dose pralidoxime. However, in contrast to our expectations, the pralidoxime-40 group showed both the highest CPP during CPR and the best resuscitation rate.

In the present study, CPP could not be brought above the threshold level for ROSC (15–20 mm Hg) with epinephrine alone,[2,4,20] resulting in sustained ROSC in only 4 of 11 animals in the control group. This might have resulted from the prolonged duration of untreated VF in our model. Multiple studies have suggested that the pressor effect of epinephrine decreases with increasing duration of arrest until the administration of epinephrine.[7,21] In the present study, the addition of pralidoxime, particularly when given in a dose of 40 mg/kg, significantly increased CPP compared with epinephrine alone and resulted in improved ROSC rates. This finding is consistent with our previous observations, suggesting potentiation of the pressor effect of epinephrine by pralidoxime.[14,15] Pralidoxime's ability to improve CPP may be

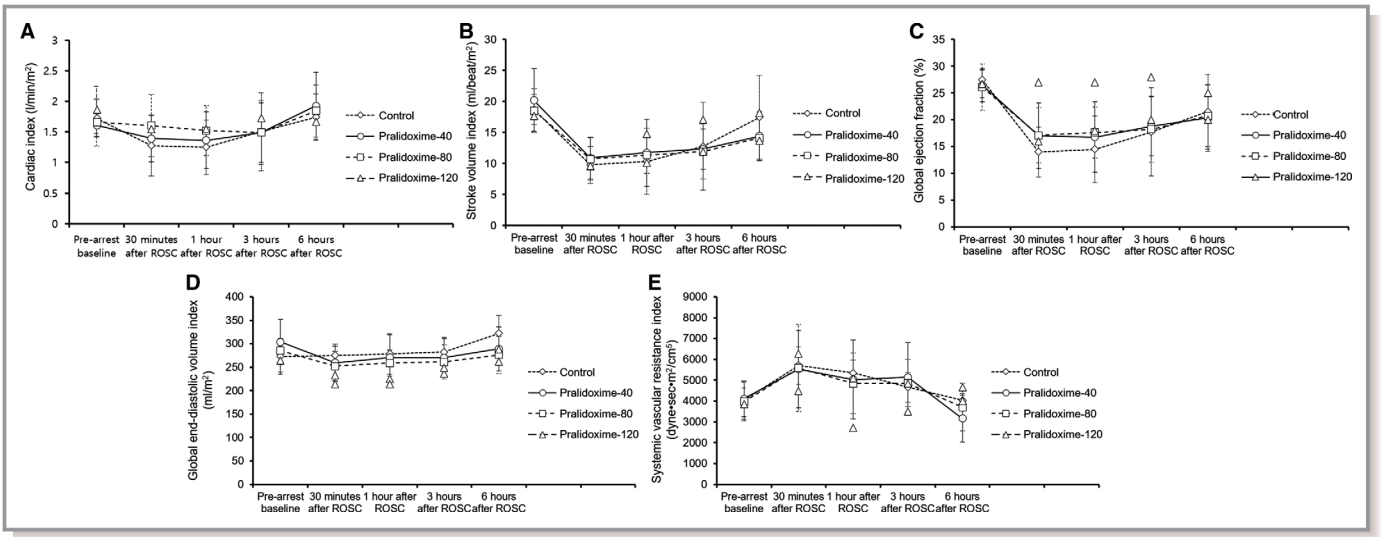


**Figure 3.** Cardiac index (**A**), stroke volume index (**B**), global ejection fraction (**C**), global end-diastolic volume index (**D**), and systemic vascular resistance index (**E**) after restoration of spontaneous circulation. Data are presented as mean±SD in the control, pralidoxime-40, and pralidoxime-80 groups. Measurements using the transpulmonary thermodilution method were obtained in 11, 9, 10, and 10 animals in the control, pralidoxime-40, pralidoxime-80, and pralidoxime-120 groups, respectively, at prearrest baseline. Among animals that were resuscitated successfully, these measurements were obtained in 4, 9, 8, and 2 animals in the control, pralidoxime-40, pralidoxime-80, and pralidoxime-120 groups, respectively, except the systemic vascular resistance index in the pralidoxime-40 group. In 1 animal in the pralidoxime-40 group, the systemic vascular resistance index was unobtainable at 30 minutes, 1 hour, and 3 hours after restoration of spontaneous circulation because of extremely low cardiac output. ROSC, restoration of spontaneous circulation.

**Table 5.** Diastolic Arterial Pressure and Heart Rate Before and After Pretreatment

| | Diastolic Arterial Pressure (mm Hg) | | Heart Rate (beats/min) | |
|---|---|---|---|---|
| | Before Pretreatment (N=7) | After Pretreatment (N=7) | Before Pretreatment (N=7) | After Pretreatment (N=7) |
| Saline+pralidoxime 40 mg/kg | 76 (73–80) | 72 (67–75) | 468 (462–492) | 468 (450–498) |
| Guanethidine+pralidoxime 40 mg/kg | 76 (70–90) | 49 (49–53)* | 456 (444–456) | 408 (390–414)* |
| Phenoxybenzamine+pralidoxime 40 mg/kg | 87 (77–91) | 43 (43–44)* | 480 (438–492) | 492 (486–492) |
| Phentolamine+pralidoxime 40 mg/kg | 98 (90–102) | 45 (42–46)* | 432 (420–450) | 384 (360–384)* |
| Saline+pralidoxime 200 mg/kg | 98 (88–102) | 93 (91–95) | 456 (450–474) | 456 (444–462) |
| Propranolol+pralidoxime 200 mg/kg | 86 (80–90) | 80 (77–88) | 420 (396–432) | 312 (306–318)* |
| Phentolamine+pralidoxime 200 mg/kg | 95 (87–101) | 37 (34–39)* | 450 (444–462) | 348 (342–426)* |

*$P<0.05$ vs before pretreatment (by Wilcoxon signed-ranks test).

attributed to its effect on peripheral vascular tone rather than its effect on myocardium. In our previous study, that investigated the effects of pralidoxime (80 mg/kg) administration during CPR on ischemia-induced left ventricular wall thickening in a pig model of out-of-hospital cardiac arrest,[14] pralidoxime had no effect on left ventricular wall thickness, left ventricular chamber area, or end-tidal carbon-dioxide level. In a recent randomized clinical trial of epinephrine in out-of-hospital cardiac arrest,[6] duration until the first dose of epinephrine was 21.5 minutes. Given this prolonged duration until epinephrine administration in clinical resuscitation, as well as the studies indicating reduced pressor effect of epinephrine after prolonged arrest,[7,21] pralidoxime appears to have the potential to benefit out-of-hospital cardiac arrest patients, in whom the administration of epinephrine is typically delayed.

In the present study, 40 mg/kg appeared to be the best dose of pralidoxime. In our previous studies,[14,15] 80 mg/kg of pralidoxime began to increase CPP 3 minutes after administration, and the difference in CPP between pralidoxime and control groups became significant 5 minutes after administration. The pressor effect of 80 mg/kg of pralidoxime in the present study was similar in onset and magnitude to that observed in these previous studies.[14,15] Meanwhile, the pressor effect of 40 mg/kg of pralidoxime began earlier and was of higher magnitude. Among the 3 doses tested in this study, only 40 mg/kg showed significantly improved CPP when compared with epinephrine alone, resulting in the highest rates of ROSC and survival.

In our first substudy, the pralidoxime-120 group had lower CPP than the control group for 3 minutes after pralidoxime administration, although the difference was not statistically significant, and showed the lowest ROSC rate among the 4 groups. To determine whether high-dose pralidoxime has a paradoxical vasodepressor action, we studied the effect of 200 mg/kg of pralidoxime on diastolic arterial pressure in anesthetized normal rats and observed an immediate and profound fall in arterial pressure that lasted ≈3 minutes, which corresponded well with the timing of the decrease in CPP after high-dose pralidoxime in the first substudy. These observations suggest that pralidoxime, when administered in high dose, has a vasodepressor effect and thus can be detrimental to cardiac arrest patients. Given the previous studies suggesting involvement of the sympathetic nervous system in the pressor action of pralidoxime,[10,11] we initially suspected that peripheral β-2 adrenergic receptor stimulation would be the mechanism responsible for the vasodepressor action of high-dose pralidoxime. However, peripheral β-2 adrenergic receptors do not appear to be involved in the vasodepressor action of high-dose pralidoxime because pretreatment with propranolol failed to abolish the initial vasodepressor effect of 200 mg/kg of pralidoxime in the second substudy.

In our second substudy, we first examined the effects of pretreatments with adrenergic antagonists on the pressor action of 40 mg/kg of pralidoxime to determine the involvement of α-adrenergic receptors in the pressor action of pralidoxime. Consistent with previous studies,[10,11] phenoxybenzamine completely blocked the pressor response produced by pralidoxime. However, pretreatment with guanethidine or phentolamine showed somewhat disconcerting results. Neither guanethidine nor phentolamine blocked the pressor response elicited by pralidoxime. Given the ability of phenoxybenzamine to block multiple types of receptors, such as muscarinic and serotonergic receptors, this finding suggests that the pressor action of pralidoxime may not be mediated through stimulation of the α-adrenergic receptors. In fact, the pressor effect of pralidoxime was greater after pretreatment with guanethidine or phentolamine. Both guanethidine and phentolamine pretreatments revealed a pressure peak at 1 minute following administration of 40 mg/kg of pralidoxime. The pressure response to

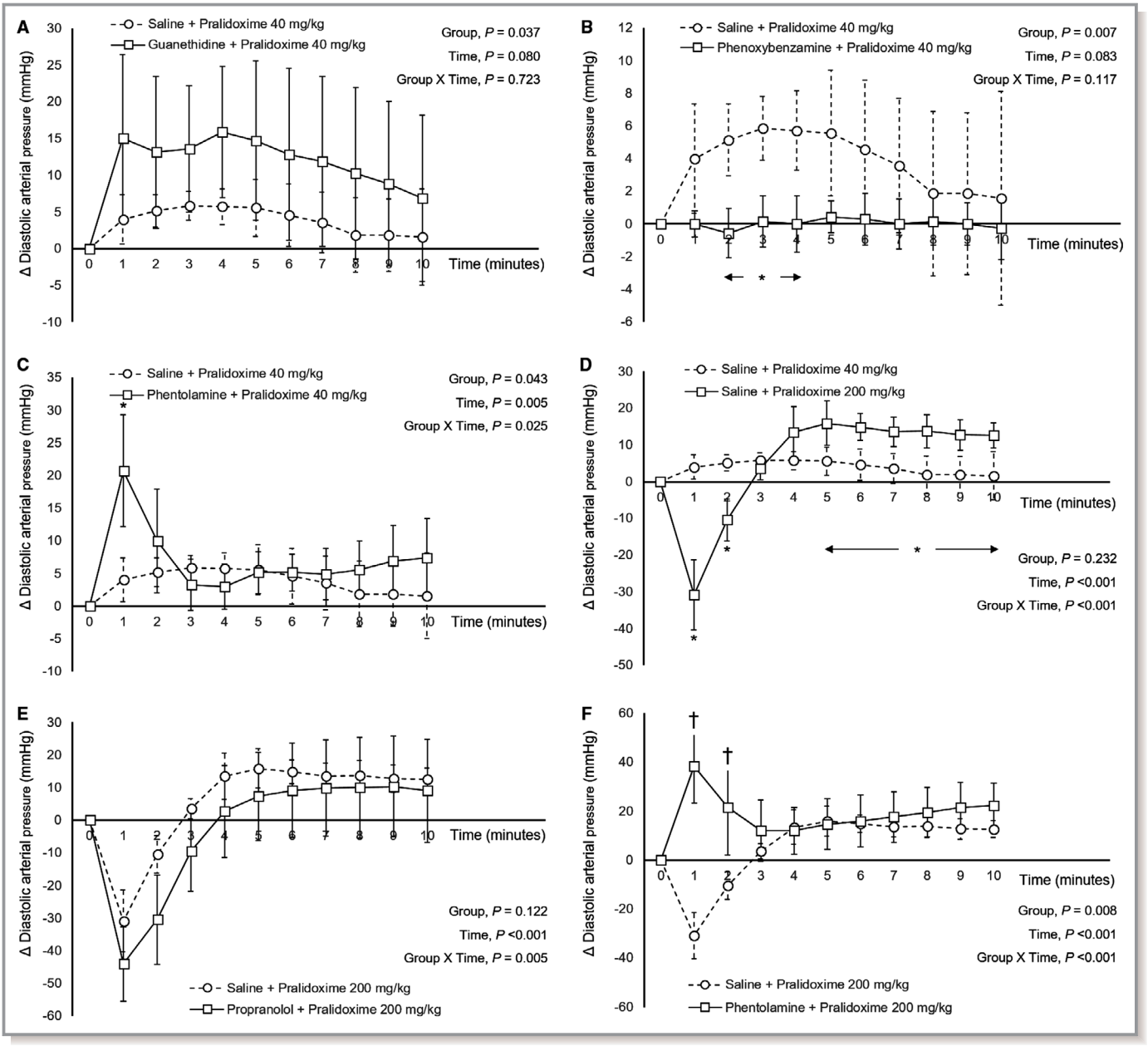


**Figure 4.** Changes in diastolic arterial pressure produced by administration of 40 (**A** through **C**) or 200 mg/kg (**D** through **F**) of pralidoxime after pretreatment with saline, guanethidine, phenoxybenzamine, phentolamine, or propranolol. Data are presented as mean±SD. Note that, for comparative purposes, the same data are illustrated for the saline+pralidoxime 40 mg/kg group (**A** thorugh **D**) and for the saline+pralidoxime 200 mg/kg group (**D** through **F**). **P*<0.05 vs the saline+pralidoxime 40 mg/kg group; †*P*<0.05 vs the saline+pralidoxime 200 mg/kg group.

pralidoxime after phentolamine pretreatment was almost identical even in rats that received 200 mg/kg of pralidoxime, the pressure response of which after saline pretreatment was of a biphasic nature consisting of an initial sharp decrease in arterial pressure followed by a delayed increase. These findings imply that this drug indeed has a dose-dependent vasodepressor action by mechanisms dependent on intact α-adrenergic receptor function, and thus the pressor effect of pralidoxime was greater when sympathetic effects were removed by adrenergic antagonists. Our findings, taken together, indicate that the pressor effect of pralidoxime, which is independent of the sympathetic nervous system, is buffered by its vasodepressor action mediated by inhibition of the sympathetic nervous system.

Admittedly, achieving sustained ROSC is just the first step toward the end goal of long-term survival with favorable neurological outcome. A drug to be used during CPR should ideally cause no harm after ROSC. In our first substudy,

hemodynamic and laboratory variables after ROSC appeared similar across the groups throughout the 6-hour intensive care period, although statistical comparisons could not be made because of the low number of animals that survived in the control and pralidoxime-120 groups. Several experimental studies have suggested that α-adrenergic stimulation impairs cerebral microcirculation, which, in turn, increases the severity of cerebral ischemia during and after CPR.[22,23] Considering the sympathoinhibitory effects of pralidoxime observed in our study, pralidoxime, when used as an adjuvant drug to potentiate the pressor effect of epinephrine, may increase CPP and thereby improve chances of achieving ROSC compared with epinephrine alone without deleterious effects on cerebral microcirculation. A study to determine the effects of pralidoxime on cerebral microcirculation is currently underway in our laboratory.

Our study has several limitations. First, it is uncertain whether the results from our animal study can be translated to humans. Second, animals were anesthetized, and thus the effects of the anesthetic agents cannot be excluded. Third, VF was electrically induced and not preceded by an ischemic insult in our study. Thus, it may be difficult to extrapolate our findings into clinical settings, where a majority of patients with sudden cardiac arrest have underlying coronary artery disease. However, higher CPP achieved by administration of pralidoxime, although not proven in our study, may be advantageous even in the presence of coronary artery occlusion. Fourth, we did not measure myocardial blood flow. However, the improvement in ROSC rate in the pralidoxime-40 group indicates that higher CPP in the pralidoxime-40 group likely resulted in higher myocardial blood flow during CPR. Fifth, we could not elucidate the mechanistic effect of pralidoxime at the receptor level. A clear understanding of its pressor action mechanism is an essential precursor to its clinical application. Hence, further studies on this mechanism are needed. Sixth, the ultimate goal of resuscitation interventions is survival with good neurological function. However, our study did not investigate the effects of pralidoxime on long-term survival or neurological outcomes. Further studies are needed to determine the effects of pralidoxime on long-term survival with favorable neurological outcomes.

## Conclusions

In a pig model of cardiac arrest, 40 mg/kg of pralidoxime administered with epinephrine led to significantly higher rates of ROSC and 6-hour survival by improving CPP during CPR, whereas 120 mg/kg did not improve CPP or rate of ROSC. Our findings suggest that the pressor effect of pralidoxime is unrelated to α-adrenoceptors, and that this pressor effect is buffered by its vasodepressor action mediated by inhibition of the sympathetic nervous system.

## Acknowledgments

We thank Editage (www.editage.co.kr) for English-language editing.

## Sources of Funding

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT; NRF-2018R1A2B6001388).

## Disclosures

None.

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