

Effects of Polyethylene Glycol-20k on Coronary Perfusion Pressure and Postresuscitation Myocardial and Cerebral Function in a Rat Model of Cardiac Arrest

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Background—Epinephrine increases the rate of return of spontaneous circulation. However, it increases severity of postresuscitation myocardial and cerebral dysfunction and reduces duration of survival. We investigated the effects of aortic infused polyethylene glycol, 20 000 molecular weight (PEG-20k) during cardiopulmonary resuscitation on coronary perfusion pressure, postresuscitation myocardial and cerebral function, and duration of survival in a rat model of cardiac arrest.

Methods and Results—Twenty-four male rats were randomized into 4 groups: (1) PEG-20k, (2) epinephrine, (3) saline control–intravenous, and (4) saline control–intra-aortic. Cardiopulmonary resuscitation was initiated after 6 minutes of untreated ventricular fibrillation. In PEG-20k and Saline-A, either PEG-20k (10% weight/volume in 10% estimated blood volume infused over 3 minutes) or saline was administered intra-aortically after 4 minutes of precordial compression. In epinephrine and placebo groups, either epinephrine (20 µg/kg) or saline placebo was administered intravenously after 4 minutes of precordial compression. Resuscitation was attempted after 8 minutes of cardiopulmonary resuscitation. Sublingual microcirculation was measured at baseline and 1, 3, and 5 hours after return of spontaneous circulation. Myocardial function was measured at baseline and 2, 4, and 6 hours after return of spontaneous circulation. Neurologic deficit scores were recorded at 24, 48, and 72 hours after return of spontaneous circulation. Aortic infusion of PEG-20k increased coronary perfusion pressure to the same extent as epinephrine. Postresuscitation sublingual microcirculation, myocardial and cerebral function, and duration of survival were improved in PEG-20k ($P<0.05$) compared with epinephrine ($P<0.05$).

Conclusions—Aortic infusion of PEG-20k during cardiopulmonary resuscitation increases coronary perfusion pressure to the same extent as epinephrine, improves postresuscitation myocardial and cerebral function, and increases duration of survival in a rat model of cardiac arrest. (*J Am Heart Assoc.* 2020;9:e014232. DOI: 10.1161/JAHA.119.014232.)

Key Words: cerebral function • coronary perfusion pressure • myocardial function • polyethylene glycol-20k • postresuscitation

Sudden cardiac arrest (SCA) is a major health issue in the United States. More than 356 000 out-of-hospital SCAs occur annually; survival to hospital admission after emergency

medical services–treated SCA was 29%, but survival to hospital discharge was only 10.8% among adults.¹ Epinephrine is the primary drug administered during cardiopulmonary resuscitation (CPR). Its effects on α -adrenergic receptors increase coronary perfusion pressure and rate of spontaneous circulation. Studies have demonstrated that use of epinephrine for SCA increased the rate of return of spontaneous circulation (ROSC) and survival to hospital admission. However, this was not associated with a significant increase in long-term survival or a favorable neurologic outcome.

A prospective observational study using national registry data in Japan² demonstrated that use of prehospital epinephrine was significantly associated with increased chance of ROSC before hospital arrival but decreased chance of survival and good neurologic outcomes 1 month after the event. In a randomized, double-blind trial, Perkins et al³ demonstrated that the use of epinephrine resulted in a significantly greater rate of ROSC than placebo; however, the

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Clinical Perspective

What Is New?

- Aortic infusion of polyethylene glycol, 20 000 molecular weight during precordial compression increases coronary perfusion pressure to the same extent as epinephrine in a rat model of cardiac arrest.
- Polyethylene glycol, 20 000 molecular weight significantly improved postresuscitation myocardial and cerebral function and duration of survival in a rat model of cardiac arrest.

What Are the Clinical Implications?

- Polyethylene glycol, 20 000 molecular weight is a potential new therapeutic for increasing rate of return of spontaneous circulation and increasing myocardial and cerebral perfusion during cardiopulmonary resuscitation.

rate of survival with a favorable neurologic outcome among patients in the epinephrine group was no different from that with placebo. Previous studies have also demonstrated that epinephrine significantly increases the severity of postresuscitation (PR) myocardial dysfunction.⁴ In addition, increases in ventricular arrhythmias, impaired cerebral microcirculation, and increased oxygen consumption are also reported with the use of epinephrine.^{5,6}

Myocardial and cerebral perfusion during CPR are overriding factors for outcomes of CPR. Polyethylene glycol–20 000 molecular weight (PEG-20k), a hybrid molecule, acts as both a colloid and a cell impermeant, has been shown to effectively expand the vascular space, and move water out of the interstitial space to stimulate thirst in pigeons and rats.⁷ PEG-20k also has been shown to improve outcomes in a rat model of hemorrhagic shock,^{8,9} where it significantly improves survival, capillary blood flow, and local oxygen delivery. Similar effects are observed in a porcine models.^{10,11} Our previous study demonstrated that administration of PEG-20k following CPR improved PR myocardial and cerebral function.¹² In this study we investigated the effects of PEG-20k on myocardial perfusion during CPR. We hypothesized that PEG-20k injected into the aorta during CPR would lead to a sudden volume expansion, which consequently increases coronary perfusion pressure and myocardial perfusion. This, in turn, improves the outcomes of CPR.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. All studies were conducted under a protocol approved by the

Institutional Animal Care and Use Committee of Virginia Commonwealth University (AD10001396). Animals received humane care in compliance with the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health.

Animal Preparation

Male Sprague-Dawley rats weighing 450 to 550 g were utilized. After induction of anesthesia with inhalation of CO₂ for 30 seconds, the animals were anesthetized by intraperitoneal injection of pentobarbital (45 mg/kg). Additional doses (10 mg/kg) were administered when required to maintain anesthesia. After no response to stimuli, animals were shaved. The trachea was orally intubated with a 14G cannula mounted on a blunt needle (Abbocath-T; Abbott Hospital Products Division, North Chicago, IL) with a 145° angled tip. End-tidal CO₂ was continuously monitored with a side-stream infrared CO₂ analyzer (Capstar-100 Carbon Dioxide Analyzer; CWE, Ardmore, PA) interposed between the tracheal cannula and ventilator.

A conventional lead II ECG was continuously monitored. Through the left external jugular vein, a PE-50 catheter (Becton Dickinson, Sparks, MD) was advanced into the right atrium for measurement of right atrial pressures. A 3F catheter (Model C-PMS-301J; Cook Critical Care, Bloomington, IN) was advanced through the right external jugular vein into the right ventricle for the induction of ventricular fibrillation (VF). For blood pressure measurements within the descending aorta and PEG-20k administration, PE-50 catheters were advanced from the left femoral artery and the right femoral artery, respectively.

A PE-50 catheter was advanced into the inferior vena cava from the right femoral vein for saline or epinephrine injection. A thermocouple microprobe (IT-18; Physitemp Instruments Inc, Clifton, NJ) was inserted into the left femoral vein for measurement of blood temperature. A precurved guidewire supplied with the catheter was then advanced into the right ventricle to induce VF. Placement of the guidewire was confirmed by an endocardial electrocardiograph. All catheters were flushed intermittently with saline containing 2.5 IU/mL of crystalline bovine heparin. During the experiment, blood temperature was maintained at 37±0.5°C by a warming surgical board.

Experimental Procedures

Twenty-four male rats were randomized into 4 groups: (1) PEG-20k, (2) epinephrine, (3) saline control–intravenous, and (4) saline control–intra-aortic. For PEG-20k and saline control–intra-aortic, either PEG-20k (10% weight/blood volume, 1.8 mL) or normal saline (1.8 mL) was administered

after 4 minutes of precordial compression (PC) by continuous arterial infusion for 3 minutes with an infusion pump. For epinephrine and placebo groups, either epinephrine (20 µg/kg) or normal saline was administered after 4 minutes of PC by continuous intravenous infusion for 3 minutes with an infusion pump (GenieTouch; Kent Scientific, Torrington, CT). The investigators were blinded to group randomization.

Fifteen minutes before induction of VF, baseline measurements, sublingual microcirculation, and echocardiography were obtained. Mechanical ventilation was established at a tidal volume of 0.6 mL/100 g of body weight, a frequency of 100 breaths/min, and fraction of inspired O₂ of 0.21. VF was then induced through a guide wire advanced into the right ventricle. A progressive increase in 60-Hz current to a maximum of 3.5 mA was then delivered to the right ventricular endocardium. Mechanical ventilation was discontinued after onset of VF. The current was continued for 3 minutes to prevent spontaneous defibrillation. After 6 minutes of untreated VF, PC and mechanical ventilation (tidal volume 0.6 mL/100 g body weight, frequency 100 breaths/min, fraction of inspired O₂ 1.0) were initiated using a pneumatically driven mechanical chest compressor.

PC was maintained at a rate of 200/min and synchronized to provide a compression/ventilation ratio of 2:1 with equal compression and relaxation for a duration of 8 minutes. Defibrillation was attempted with up to 3 4-J countershocks. If ROSC, defined as the return of mean aortic pressure above 50 mm Hg for 5 minutes, was not achieved after the first defibrillation attempt, a 30-second interval of CPR was performed before the next defibrillation attempt (up to 3 attempts). After ROSC, a fraction of inspired O₂ of 1.0 was continued for 1 hour, adjusted to 0.5 for the second hour, and 0.21 thereafter.

Measurements

ECG, aortic and right atrial pressures, end-tidal CO₂, and blood temperature values were continuously recorded on a personal computer-based data acquisition system supported by WINDAQ software (DATAQ, Akron, OH). Coronary perfusion pressure (CPP) was calculated as the difference in time-coincident diastolic aortic and right atrial pressures that were displayed in real time. Sublingual microcirculation was measured at baseline and 1, 3, and 5 hours after ROSC using a side-stream dark-field imaging device (MicroScan; Microvision Medical, Amsterdam, the Netherlands) that had a ×5 imaging objective, resulting in an on-screen magnification of ×276. Three discrete fields for each were captured with the intention to minimize motion artifacts. Microcirculatory flow index (MFI) was measured using the method of Spronk et al.¹³ The image was divided into 4 quadrants, and predominant flow type (absent=0, intermittent=1, sluggish=2,

normal=3) was assessed in the small vessels of each quadrant, which was <20 µm in diameter.

The MFI score represented the average values of the 4 quadrants. Perfused vessel density (PVD) was quantitated based on the method of De Backer et al.¹⁴ Vessel density was calculated as the number of vessels crossing the catheters divided by the total length of the catheters. Myocardial function, including cardiac output (CO), ejection fraction, and myocardial performance index (MPI) was measured at baseline and 2, 4, and 6 hours after ROSC by echocardiography (HD11XE; Philips Medical Systems, Eindhoven, the Netherlands) with a 12.5-Hz transducer. CO and ejection fraction were used to estimate myocardial contractility; MPI was used to estimate left ventricular diastolic function. MPI is the sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time. MPI was derived as (a–b)/b, where “a” is the measured duration from mitral closure to opening, and “b” is the aortic flow ejection time. Neurologic deficit score (NDS), which ranged from 0 (no observed neurologic deficit) to 500 (death or brain death), was used to evaluate neurologic function. The NDS was examined at 24, 48, and 72 hours after ROSC.

Statistical Analyses

All data are presented as mean±SE of the mean. The outcome variables were examined for normality with a Shapiro-Wilk test. All data were normally distributed. For measurements between groups, ANOVA and the Bonferroni method were used. Comparisons between time-based measurements within each group were performed by ANOVA with the Bonferroni post hoc test. A log-rank (Mantel-Cox) test was used for survival analysis. A value of *P*<0.05 was regarded as significant.

Results

Twenty-four rats were successfully resuscitated and included for analysis. There were no significant differences in body weight and baseline measurements, including hemodynamic data, blood temperature, end-tidal CO₂, myocardial function (ejection fraction, CO, and MPI), and sublingual microcirculation (MFI and PVD) between groups. In saline placebo and saline–intra-aorta, the CPP was not significantly increased. However, arterial injection of PEG-20k significantly increased coronary perfusion pressure compared with saline placebo or saline–intra-aorta (*P*<0.05). PEG-20k did not reach statistical significance when compared with epinephrine in increasing CPP (Figure 1). Duration of arrhythmia in the epinephrine group was much longer than that in the PEG-20k group (*P*<0.05) (Table).

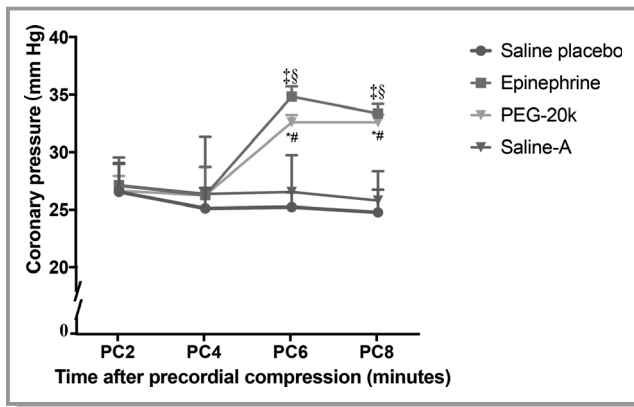


Figure 1. Coronary perfusion pressure changes during CPR. * $P < 0.0001$ vs PEG-20k with saline placebo; # $P < 0.0001$ vs PEG-20k with Saline-A; ‡ $P < 0.0001$ vs epinephrine with saline placebo; § $P < 0.0001$ vs epinephrine with Saline-A. Values are presented as the mean ± SE. n=6 in each group. CPR indicates cardiopulmonary resuscitation; PEG-20k, polyethylene glycol with 20 000 molecular weight; Saline-A, saline infused intra-aortically.

After resuscitation, myocardial function as measured by CO, ejection fraction, and MPI was significantly impaired in all groups compared with baseline. PEG-20k treatment during PC significantly improved the severity of PR myocardial function compared with other groups ($P < 0.05$). Epinephrine increased the severity of PR myocardial dysfunction when compared with saline placebo and saline-intra-aorta ($P < 0.05$) (Figure 2). Sublingual microcirculation was significantly reduced after successful resuscitation in all groups compared with baseline. PEG-20k treatment also significantly increased PVD and MFI values compared with other groups ($P < 0.05$). However, PVD and MFI values were significantly decreased compared with saline placebo and saline-intra-aorta in the epinephrine treatment group. ($P < 0.05$) (Figure 3).

Duration of survival with PEG-20k was significantly improved compared with those of other groups ($P < 0.05$). Four rats survived 72 hours in the PEG-20k group, no rats survived through the entire 72 hours in saline-placebo or

Table. Number of Defibrillations and Arrhythmia Duration

Group	Number of Defibrillations	Arrhythmia Duration
Saline placebo	2.00 ± 0.89	9.67 ± 5.32
Epinephrine	5.50 ± 2.88 ^{†‡§}	14.00 ± 5.35 [†]
PEG-20k	1.33 ± 0.52	3.17 ± 3.06
Saline-A	2.33 ± 0.82	10.67 ± 6.68

PEG-20k indicates polyethylene glycol with molecular weight 20 000; Saline-A, aortic infused saline.

[†] $p < 0.05$ vs PEG-20k with Epinephrine.

[‡] $p < 0.0001$ vs Epinephrine with Saline placebo.

[§] $p < 0.05$ vs Epinephrine with Saline-A.

Values are presented as the mean ± standard error.

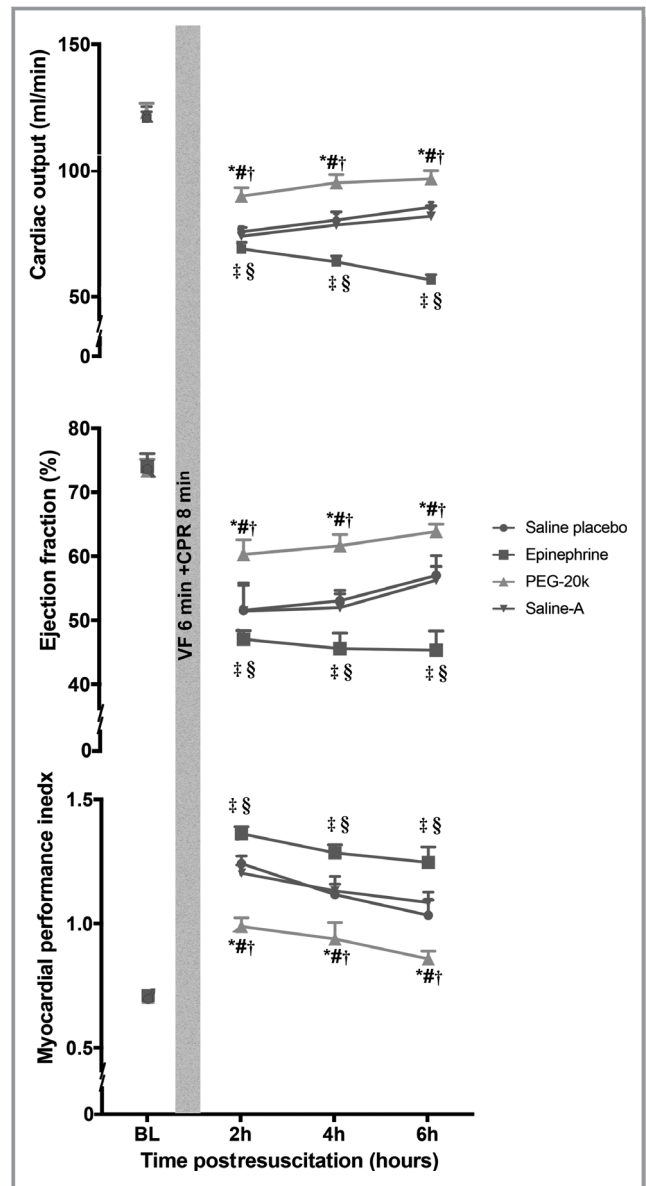


Figure 2. Polyethylene glycol with molecular weight 20 000 (PEG-20k) improves postresuscitation myocardial function. * $P < 0.05$ vs PEG-20k with saline placebo; # $P < 0.05$ vs PEG-20k with Saline-A; † $P < 0.05$ vs PEG-20k with epinephrine; ‡ $P < 0.05$ vs epinephrine with saline placebo; § $P < 0.05$ vs epinephrine with Saline-A. Values are presented as the mean ± SE. n=6 in each group. BL indicates baseline; CPR, cardiopulmonary resuscitation; Saline-A, saline infused intra-aortically; VF, ventricular fibrillation.

saline-intra-aorta groups, and only 1 rat survived more than 24 hours in the epinephrine group (Figure 4). PR neurologic function was assessed by NDS. Lower NDS values were observed in PEG-20k compared with the corresponding saline controls and epinephrine at 24 hours after resuscitation ($P < 0.05$). NDS values were significantly decreased in PEG-20k compared with other groups at 48 and 72 hours after resuscitation (Figure 5). Rats treated with PEG-20k during

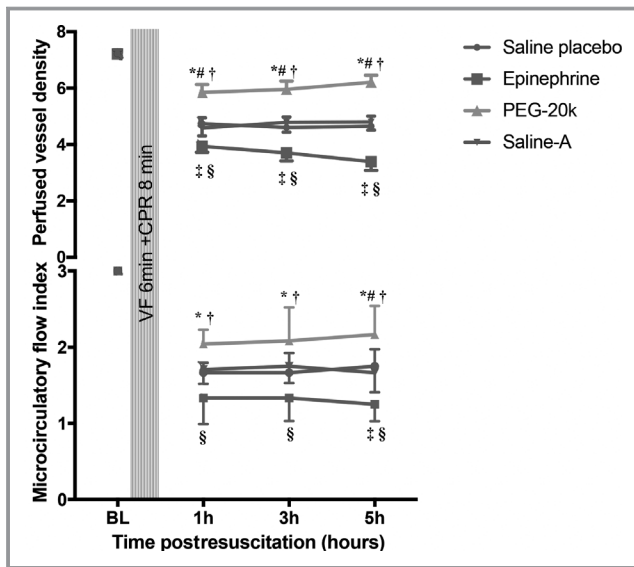


Figure 3. Polyethylene glycol with molecular weight 20 000 (PEG-20k) improves sublingual microcirculation. * $P<0.05$ vs PEG-20k with saline placebo; # $P<0.05$ vs PEG-20k with Saline-A; † $P<0.05$ vs PEG-20k with epinephrine; ‡ $P<0.05$ vs epinephrine with saline placebo; § $P<0.05$ vs epinephrine with Saline-A. Values are presented as the mean±SE. n=6 in each group. BL indicates baseline; CPR, cardiopulmonary resuscitation; Saline-A, saline infused intra-aortically; VF, ventricular fibrillation.

PC significantly reduced severity of PR neurologic dysfunction compared with other groups ($P<0.05$).

Discussion

The present study demonstrated that aortic infusion of PEG-20k significantly increased CPP to the same extent as epinephrine during CPR. However, the severity of myocardial and neurologic dysfunction was significantly less in animals

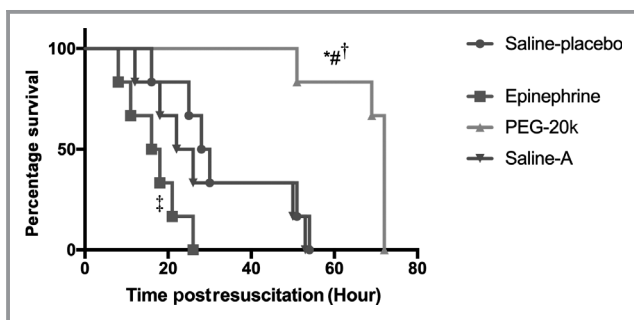


Figure 4. Polyethylene glycol with molecular weight 20 000 (PEG-20k) improves survival duration. * $P=0.0022$ vs PEG-20k with saline placebo; # $P=0.0016$ vs PEG-20k with Saline-A; † $P=0.0005$ vs PEG-20k with epinephrine; ‡ $P=0.012$ vs saline placebo with epinephrine. Values are presented as the mean±SE. n=6 in each group.

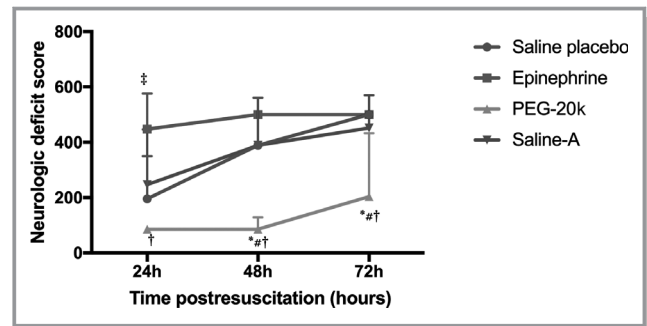


Figure 5. Polyethylene glycol with molecular weight 20 000 (PEG-20k) improves postresuscitation cerebral function. At 24 hours, ‡ $P=0.0084$ vs epinephrine with saline placebo, † $P<0.0001$ vs PEG-20k with epinephrine; at 48 hours, * $P=0.001$ vs PEG-20k with saline placebo, † $P<0.0001$ vs PEG-20k with epinephrine; at 72 hours, * $P=0.0014$ vs PEG-20k with saline placebo, # $P=0.0095$ vs PEG-20k with Saline-A, † $P=0.0014$ vs PEG-20k with epinephrine. Values are presented as the mean±standard error. n=6 in each group.

treated with PEG-20k, with improved duration of survival compared with epinephrine-treated animals.

Early and effective CPR is a crucial component of successful resuscitation. The life-saving intervention employs chest compressions and ventilation to maintain a level of cardiocerebral blood flow until the interdependent functions of the heart, brain, and lungs are restored with ROSC.

For successful resuscitation, a critical level of marginal myocardial blood flow must be obtained to deliver oxygen and improve the metabolic state of the myocardium.^{15,16} CPP represents the gradient that drives coronary blood pressure, the difference between the diastolic aortic pressure and the left ventricular end-diastolic pressure. It is well established that a greater CPP and the consequent increased myocardial flow are strongly correlated with increased rate of ROSC.^{16,17} CPP has been a golden standard of the success of resuscitation.

Epinephrine has been a key component of advanced life support algorithms for more than 5 decades. Its α -adrenergic receptor stimulation has been shown to be most beneficial during CPR. The stimulation of α receptors in vascular smooth muscle causes vasoconstriction, which increases the aortic diastolic pressure, CPP, and the rate of ROSC. However, the α_1 and β -adrenergic effects of epinephrine have adverse effects on outcomes. In 1995 Tang et al⁴ demonstrated that reversal of global myocardial ischemia after cardiac resuscitation is followed by myocardial dysfunction in a rat model of cardiac arrest and resuscitation. Its severity is increased with increasing duration of untreated cardiac arrest. Epinephrine significantly increases the severity of PR myocardial dysfunction with consequent reduction in duration of PR survival when compared with the selective α_1 -agonist phenylephrine and after epinephrine was combined with a β_1 -blocking agent (esmolol).^{4,5}

Subsequent studies have confirmed that epinephrine increases the severity of PR myocardial dysfunction and myocardial tissue injury.^{18,19} Our experimental results are also consistent with clinical trials that showed that epinephrine did not result in better short-term survival or hospital discharge rate.^{2,3} Due to the deleterious effects of epinephrine, the use of a nonadrenergic agent such as vasopressin in cardiac arrest was proposed as an alternative or as an adjunct. Vasopressin produces vasoconstriction by directly stimulating smooth muscle V₁ receptors. However, its efficacy was doubted compared with epinephrine.²⁰⁻²³

PEG-20k is a hybrid molecule that acts as a partial colloid with cell-impermeant effects as some of the material (30%) leaves the capillary space into the interstitium.¹¹ PEG-20k has been shown to significantly reduce ischemia-induced cell swelling, increase tolerance to the low-volume state, improve capillary blood flow, and increase survival in rodent shock models and a preclinical porcine model.^{9,24} PEG-20k acts as an impermeant to prevent water movement into the cell, and a large portion of the molecule stays behind in the capillary to exert oncotic force that draws the interstitial water into the capillary. PEG-20k presents a greater hydrodynamic volume than would be expected from its molecular weight due to its high flexibility and hydrophilicity and the large number of water molecules coordinated by its chains. The capillary oncotic reflection coefficient for PEG-20k indicates a hybrid nature of the molecule.²⁴ This establishes multiple osmotic gradients in the microcirculation that may account for its rapid water-transfer properties. Administration of PEG-20k solutions has a significant effect on the expansion of blood volume because a large portion of the molecules stay behind in the capillary to exert an oncotic force that draws the interstitial water into the capillary, which may lead to increased coronary perfusion pressure during PC as observed in the present study. However, this effect may differ from that of hypertonic saline, which has a transient osmotic effect because sodium quickly moves into the cell down its concentration gradient when the sodium pump shuts off during ischemia (CPR), and this exacerbates cell swelling and microcirculatory no-flow.

Following cardiac arrest, the microvascular permeability increases, and the filtration rate exceeds the myocardial lymph flow, resulting in fluid accumulation. During the compressing phase, reperfusion-induced or ischemic contracture decreases myocardial compliance, which further enhances the formation of myocardial edema and compromises the effectiveness of CPR.²⁵ The osmotic effect of PEG-20k may decompress the microcirculation by preventing metabolic cell swelling, which further enhances capillary perfusion by decreasing resistance to flow.⁹ This also increases the myocardial compliance and enhances the effectiveness of CPR. In this study PEG-20k treatment

significantly increased PVD and MFI values compared with other groups ($P<0.05$), which indicates that PEG-20k may ameliorate microcirculation defects during CPR and increase the myocardial compliance and oxygen exchange.

The mechanisms by which aortic infusion of PEG-20k rapidly increases CPP remain to be investigated. First, a rapid direct expansion of the aortic volume of PEG-20k is likely a potential explanation of increased CPP. Second, the osmotic effect of PEG-20k may decompress microcirculation and further enhance capillary perfusion, which increases the myocardial contractility and compliance and enhances the effectiveness of CPR. Furthermore, the interval of cardiac arrest and the extremely possible compression-mediated physiological reserve of these rats may have preserved vascular tone, which in turn enhanced the volume-expanding effects of PEG-20k and venous return. Our study observed salutary effects of PEG-20k on coronary perfusion pressure during CPR and PR myocardial and cerebral function in a rat model of cardiac arrest and resuscitation.

Consistent with our previous study,¹² duration of survival in animals treated with PEG-20k was significantly improved. The NDS score that represents cerebral function was significantly improved compared with epinephrine-treated animals. PEG-20k solution pulls isotonic fluid out of the extravascular space, thereby decompressing and filling capillaries, which improves oxygen delivery. Increased cerebral blood flow is associated with improved neurologic outcomes,²⁶ and PEG-20k improves cerebral capillary blood flow in low-volume states.⁹

There are some limitations in this study. First, the experiments were performed in animals without any underlying disease. Second, PEG-20k was administered at PC 4, which may not be applicable to human victims. Third, in this study, we found that aortic infusion of PEG-20k during CPR increases CPP to the same extent as epinephrine, and the mechanisms by which aortic infusion of PEG-20k rapidly increases CPP remain to be investigated in future studies. Fourth, the sample size of the present study was relatively small.

Conclusions

Aortic infusion of PEG-20k during PC increases coronary perfusion pressure to the same extent as epinephrine but with improved PR myocardial and cerebral function and duration of survival in a rat model of cardiac arrest. It may be a new option for increasing myocardial and cerebral perfusion during CPR.

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Disclosures

None.

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