The effects of epinephrine on outcomes of normothermic and therapeutic hypothermic cardiopulmonary resuscitation*

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Objective: **To investigate the effects of epinephrine when administered during either normothermic or therapeutic hypothermic cardiopulmonary resuscitation on postresuscitation myocardial and cerebral function and survival.**

Design: **Prospective, randomized, placebo-controlled experimental study.**

Setting: **University-affiliated animal research laboratory.**

Subjects: **Thirty-two healthy male Sprague-Dawley rats.**

Interventions: **Ventricular fibrillation was induced and untreated for 8 mins. The animals were then randomly assigned to one of four groups: normothermic placebo control; normothermic epinephrine; hypothermic placebo control; and hypothermic epinephrine. Hypothermia was initiated coincident with the start of cardiopulmonary resuscitation. The blood temperature was reduced and maintained at 32 ± 0.2°C and continued for 4 hrs after resuscitation. Normothermic animals were maintained at 37 ± 0.2°C. Either placebo or epinephrine (20 μg/kg) was administered 5 mins after the start of cardiopulmonary resuscitation and 3 mins before defibrillation.**

Measurements and Main Results: **Postresuscitation cardiac output, ejection fraction, and myocardial performance index were measured hourly for 4 hrs after resuscitation; neurologic deficit scores were measured daily for 7 days, and durations of survival were observed for up to 3 mos. Except for three normothermic control animals, all animals were resuscitated. When epinephrine was administered during normothermic cardiopulmonary resuscitation, postresuscitation myocardial function was severely impaired when compared with the normothermic control group. However, postresuscitation myocardial function was significantly better in animals treated with epinephrine during hypothermic cardiopulmonary resuscitation when compared with hypothermic controls. This was associated with significantly fewer postresuscitation ventricular arrhythmias, less ST-segment elevation, better postresuscitation neurologic deficit scores, and longer duration of survival.**

Conclusions: **Epinephrine, when administered during normothermic cardiopulmonary resuscitation, significantly increases the severity of postresuscitation myocardial dysfunction and decreases the duration of survival. These detrimental effects of epinephrine, however, no longer exist when it is administered during therapeutic hypothermic cardiopulmonary resuscitation. (Crit Care Med 2010; 38:2175–2180)**

KEY WORDS: cardiopulmonary resuscitation; epinephrine; hypothermia; postresuscitation; survival

In the United States, approximately one million deaths each year are attributable to cardiovascular disease. Of these deaths, approximately one-third, or 350,000, occur suddenly and outside of the hospital. Although the initial success of cardiopulmonary resuscitation (CPR) is approximately 39% (range from 13% to 59%), a majority of victims die within 72 hrs, primarily due to heart failure and/or recurrent ventricular fibrillation (VF). CPR itself, therefore, yields a functional survival rate of only 1.4% to 5% (1). Profound postresuscitation myocardial dysfunction is observed after an interval of 4 mins or more of untreated cardiac arrest in both laboratory and clinical studies (2–5). It is one of the major causes of the high fatality rate within the initial 72 hrs after successful resuscitation from cardiac arrest (4–6).

Epinephrine has been the recommended vasopressor agent for the treatment of human cardiac arrest for nearly 50 yrs. There is unequivocal evidence that its efficacy is attributable to its α-adrenergic vasopressor effects, which increase coronary perfusion pressure (CPP) by increasing peripheral vascular resistance. However, its β- and α_1-adrenergic effects increase both inotropic and chronotropic actions on the heart and provoke disproportionate increases in myocardial oxygen consumption and the severity of ischemic injury when the coronary blood flow is critically reduced (7). Accordingly, it increases the severity of postresuscitation myocardial contractile dysfunction and the incidence of ventricular arrhythmias, including recurrent VF, and decreases postresuscitation survival (8).

Hypothermia induced by physical cooling for the treatment of cardiac arrest is not a new therapy. However, its use in patients after cardiac arrest was repopularized by two landmark clinical studies in 2002. Clinical cooling to 33°C in comatose victims of cardiac arrest who achieved return of spontaneous circulation (ROSC) after VF was noted to have an absolute improvement in the rate of neurologically favorable survival of 16% (9, 10). In animal models of cardiac arrest, early application of hypothermia and rapid achievement of target temperature have been shown to significantly improve

*See also p. 2264.

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postresuscitation myocardial function, survival rate, and long-term neurologic outcome (11, 12). On the basis of these clinical and laboratory studies, the American Heart Association has recommended the use of hypothermia for routine management of patients after cardiac arrest following initial successful resuscitation (13).

However, current knowledge of whether there is an altered sensitivity of α- and β-adrenergic receptors during mild hypothermia is limited, especially during the low-flow states of CPR. We therefore investigated the effects of epinephrine during hypothermic CPR ("intra-CPR" hypothermia) on postresuscitation myocardial function and duration of survival. Our hypothesis was that, during the low-flow states of CPR, mild hypothermia selectively reduces the β effects of epinephrine. Intra-CPR mild hypothermia, therefore, will not reduce the vasopressor effect of epinephrine; however, it will minimize the detrimental effects of epinephrine on postresuscitation myocardial function and benefit on long-term survival.

METHODS

All animals received humane care in compliance with the *Principles of Laboratory Animal Care* and *Guide for the Care and Use of Laboratory Animals* (14, 15). The protocol was approved by the Institutional Animal Care and Use Committee of the Weil Institute of Critical Care Medicine. The animal laboratories of our institute are fully accredited by the American Association for Accreditation of Laboratory Animal Care International and the National Institutes of Health (A4145-01). Our established rodent model of cardiac arrest and resuscitation was used. Healthy male Sprague-Dawley rats, aged 6 to 8 mos, weighing between 450 and 550 g, were supplied by a single-source breeder (Harlan Sprague-Dawley, Livermore, CA), which has consistently supplied healthy animals of relatively uniform age and weight.

Thirty-two Sprague-Dawley rats were fasted overnight except for free access to water. The details of animal preparation were published previously (16). In brief, the animals were anesthetized by intraperitoneal injection of pentobarbital (45 mg/kg), and additional doses (10 mg/kg) were administrated at intervals of approximately 1 hr or when required to maintain anesthesia, except that no anesthetic agents were administered for 30 mins before induction of cardiac arrest. The trachea was orally intubated with a 14-gauge cannula. A PE-50 catheter (Becton Dickinson, Franklin Lakes, NJ) was advanced into the descending aorta from the left femoral artery for measurement of arterial pressure and sampling arterial blood. Through the left external jugular vein, another PE-50 catheter was advanced into the right atrium for measurement of right atrial pressures and for the administration of either epinephrine or placebo. This catheter was also used for sampling blood from the right atrium and blood replacement. Aortic and right atrial pressures were measured with high-sensitivity transducers (model 42584-01, Abbott Critical Care Systems, North Chicago, IL). A thermocouple microprobe, 10 cm in length and 0.5 mm in diameter (9030-12-D-34, Columbus Instruments, Columbus, OH), was inserted into the right femoral artery and advanced to the descending aorta for measurement of blood temperature. A 3-F PE catheter (model C-PMS-301J, Cook Critical Care, Bloomington, IN) was advanced through the right external jugular vein into the right atrium. A precurved guide wire supplied with the catheter was then advanced through the catheter into the right ventricle and confirmed by endocardial electrocardiogram for inducing VF. All of the catheters were flushed intermittently with saline containing 2.5 IU/mL of crystalline bovine heparin. A conventional lead II electrocardiogram was continuously monitored.

Experimental Procedures

VF was electrically induced with progressive increases in 60-Hz current to a maximum of 3.5 mA delivered to the right ventricular endocardium. The current flow was continued for 3 mins to prevent spontaneous defibrillation. Animals were randomly assigned into one of four groups (n = 8 in each group): normothermic placebo control; normothermic epinephrine; hypothermic control; and hypothermic epinephrine. Mechanical ventilation was stopped after the onset of VF. Precordial compression was begun 8 mins after the onset of untreated VF with a pneumatically driven mechanical chest compressor as previously described (16). Coincident with the start of precordial compression, the animals were mechanically ventilated at a frequency of 100/min and with an F_{IO_2} of 1.0. Precordial compression was maintained at a rate of 200 min^{-1} and synchronized to provide a compression/ventilation ratio of 2:1 with equal compression-relaxation duration (i.e., 50% duty cycle). Depth of compression was initially adjusted to secure a CPP of 22 ± 2 mm Hg. Epinephrine (20 μg/kg) or saline placebo was injected into the right atrium over a 30-sec interval, beginning 5 mins after the start of precordial compression. Resuscitation was attempted with up to three, 2-J (2) countershocks after 8 mins of CPR (Fig. 1). Resuscitation was defined as the return of supraventricular rhythm with a mean aortic pressure of 50 mm Hg for a minimum of 5 mins.

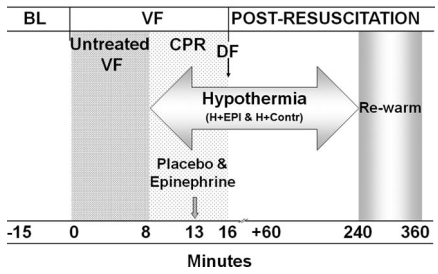

Figure 1. Experimental procedure. *H+EPI*, hypothermic epinephrine group; *H+Contr*, hypothermic control group; *BL*, baseline; *VF*, ventricular fibrillation; *DF*, defibrillation; −15, 15 mins before ventricular fibrillation was induced; *CPR*, cardiopulmonary resuscitation.

In animals assigned to therapeutic hypothermia, body cooling was initiated coincident with the start of CPR (Fig. 1). Blood temperature was reduced to 34 ± 0.2°C when epinephrine was injected and further reduced to 32 ± 0.2°C when defibrillation was attempted. Body cooling was induced with the aid of ice packs and an electrical fan (17). Once reached, the target temperature was maintained with the aid of the Blanketrol II (CSZ, Cincinnati, OH) and continued for 4 hrs after resuscitation and returned to 37°C over a rewarming period of 2 hrs. For those animals not subjected to cooling, blood temperature was maintained at 37 ± 0.2°C.

After resuscitation, mechanical ventilation was continued with 100% oxygen for 1 hr and then continued with 21% oxygen for 3 hrs more, at which time the animals had uniformly recovered from anesthesia. All catheters, including the endotracheal tube, were then removed. The animals were continuously observed by the investigators for an additional 2 hrs. The animals were returned to their cages and closely monitored for 72 hrs. For long-term survival, all resuscitated animals were observed for up to 3 mos.

Measurements

Aortic and right atrial pressures, electrocardiographic tracings, and end-tidal CO_2 were continuously recorded for up to 4 hrs after ROSC on a PC-based data-acquisition system supported by WINDAQ software (DATAQ, Akron, OH). CPP was calculated as the difference between decompression diastolic aortic and time-coincident right-atrial pressures measured at the end of each minute of precordial compression. Myocardial function was noninvasively measured at baseline and at hourly intervals after resuscitation with a Philips ultrasound system using a 12.5-Hz transducer (HD 11 XE, Philips Ultrasound,

Bothell, WA). All of the measurements, including cardiac output, myocardial performance index, and ejection fraction, were reviewed and confirmed separately by two of the investigators. The myocardial performance index was obtained as both systolic and diastolic functions and is the ratio of total time spent in isovolumic activity (isovolumic contraction and relaxation times) to the ejection time and was measured from the mitral inflow and left ventricular outflow time intervals (18, 19). The ejection fraction served as an indicator of myocardial contractility.

Resuscitated animals were monitored for 4 hrs and then observed at 24-hr intervals by a participating investigator for a total of 72 hrs. Neurologic deficit scores were scored according to the method of Hendrickx et al (20) (neurologic deficit score when normal = 0 and coma = 500). The neurologic deficit score was determined at 24, 48, and 72 hrs and at 1 wk, 1 mo, and up to 3 mos after ROSC. Myocardial functions were evaluated on the same day as the neurologic deficit score examination. For the echocardiograph measurement after ROSC, the animals were anesthetized by intraperitoneal injection of pentobarbital (20 mg/kg) 30 mins before measurement. After the 3-mo evaluation, the animals were euthanized by intraperitoneal injection of pentobarbital (150 mg/kg). Autopsy was routinely performed to identify adverse effects of the interventions.

Statistical Analyses

For measurements among groups, ANOVA and Schaffer's multicomparison techniques were used. Comparison between time-based measurements within each group was performed with ANOVA repeated measurement. The outcome differences were analyzed with Fisher's exact test. Values are reported as mean ± SD. A value of $p < .05$ was considered significant.

RESULTS

Thirty-eight rats were used for this study, six were excluded because of instrumentation or technical failure before randomization; 32 studies were performed and completed. Baseline blood temperature, myocardial function, hemodynamics, and blood analytical measurements did not differ among the four groups. There was no difference among the groups in the amount of the electrical current that was required for inducing VF. During CPR, blood temperature of all animals treated with hypothermia was reduced to 34 ± 0.2°C when epinephrine or placebo was injected and further reduced to 32 ± 0.2°C when defibrillation was attempted, as defined by the study protocol (Fig. 2). CPP was significantly increased after administration of epinephrine in both normothermic and hypothermic groups. Regardless of the significant difference in blood temperature, there was no significant difference in CPP between the two placebo control groups (Fig. 3).

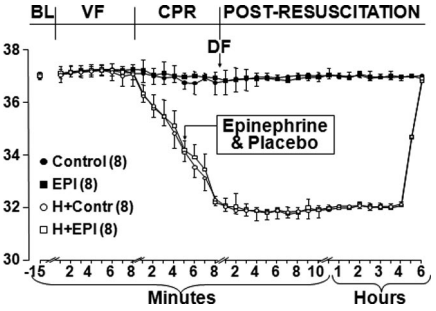

Figure 2. Blood temperature, Celsius. $p < .01$ vs. normothermic groups during hypothermia. *Control* in *closed circle*, normothermic control group; *EPI* in *closed square*, normothermic epinephrine group; *H+Contr* in *open circle*, hypothermic control group; *H+EPI* in *open square*, hypothermic epinephrine group. *BL*, baseline; *VF*, ventricular fibrillation; *DF*, defibrillation; −15, 15 mins before ventricular fibrillation was induced; *CPR*, cardiopulmonary resuscitation.

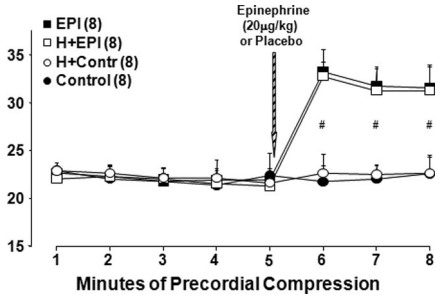

Figure 3. Coronary perfusion pressure, mm Hg. $^{\#}p < .01$ vs. both hypothermic and normothermic placebo control. *Control* in *closed circle*, normothermic control group; *EPI* in *closed square*, normothermic epinephrine group; *H+Contr* in *open circle*, hypothermic control group; *H+EPI* in *open square*, hypothermic epinephrine group.

Except for three animals in the control group, all the animals were successfully resuscitated. The incidence of postresuscitation recurrent VF/ventricular tachycardia during the first 15 mins after successful resuscitation was significantly reduced in animals treated with hypothermia, especially in the hypothermic epinephrine group (Table 1).

As we previously observed (8), myocardial function, as measured by cardiac output, ejection fraction, and myocardial performance index, was significantly impaired in all the animals after successful resuscitation when compared with the baseline values. Significantly less impairment in postresuscitation myocardial systolic and diastolic function was observed in animals treated with hypothermia (Figs. 4–6). It is interesting to note that there was significant improvement in postresuscitation myocardial function in the combination of the hypothermia- and epinephrine-treated group, which was opposite of the normothermic epinephrine-treated animals, which had significantly increased severity of postresuscitation myocardial dysfunction when compared with the normothermic control group (Figs. 4–6). Furthermore, the duration of the impairment of myocardial functions was significantly shorter in animals treated with the combination of hypothermia and epinephrine. All of the myocardial function measurements recovered to 90% of the baseline values in this group of animals within the first 60 mins and completely recovered 24 hrs after ROSC. This result contrasted with that for the remaining three groups of animals, in which the impairment of myocardial function persisted during the first 24 hrs after initial ROSC. After ROSC, there was significantly less ST-segment elevation in the hypothermic epinephrine-treated animals vs. the hypothermic control group, and once again this result was opposite that of the normothermic epinephrine-treated animals, which had significantly greater ST-segment elevation when compared with the control group (Table 2). Heart rate was consistently significantly decreased in the hypothermic groups when compared with the normothermic groups between 30 and 240 mins after resuscitation (301 ± 21 vs. 367 ± 20 at 240 mins, $p < .01$).

The durations of survival are listed in Table 3. All hypothermia-treated animals survived for >72 hrs, which contrasts with normothermic and placebo-treated animals, which survived for 41 ± 28 hrs, and the normothermic and epinephrine-treated animals, which survived for 18 ± 22 hrs ($p < .01$). There was no statistically significant difference in 3-mo survival rate between the animals treated with combination of hypothermia and epinephrine and animals treated with hypothermia and placebo (100% vs. 67%; Table 3). Significantly less postresuscitation neurologic impairment was observed in hypothermia-treated animals. Between the two groups treated with hypothermia, the animals treated with hypothermia

Table 1. Fifteen-minute postresuscitation ventricular arrhythmias

	Number of Episodes of Ventricular Fibrillation/ Ventricular Tachycardia, Mean ± SD	Number of Episodes of Salvos, Mean ± SD
Normothermic control	24 ± 21	34 ± 34
Normothermic epinephrine	43 ± 36	78 ± 91
Hypothermic control	10 ± 11[a]	16 ± 14
Hypothermic epinephrine	4 ± 8[b]	2 ± 3[c]

Salvo, a series of three to five consecutive premature ventricular contractions.

[a]$p<.05$ vs. normothermic epinephrine; [b]$p<.05$ vs. normothermic control and epinephrine; [c]$p<.05$ vs. hypothermic control, normothermic control, and epinephrine.

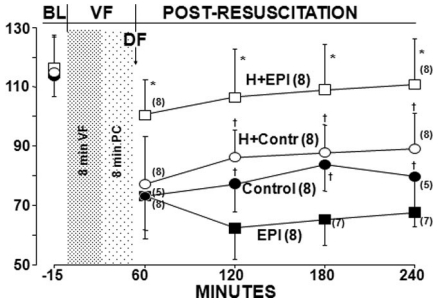

Figure 4. Cardiac output, milliliter/minute. *$p <$ .05 vs. hypothermic control, normothermic control, and epinephrine. $^{\delta}p < .05$ vs. normothermic control and epinephrine. $^{\dagger}p < .05$ vs. normothermic epinephrine. *Control* in *closed circle*, normothermic control group; *EPI* in *closed square*, normothermic epinephrine group; *H+Contr* in *open circle*, hypothermic control group; *H+EPI* in *open square*, hypothermic epinephrine group. *BL*, baseline; *VF*, ventricular fibrillation; *DF*, defibrillation; *PC*, precordial compression; −15, 15 mins before ventricular fibrillation was induced; *CPR*, cardiopulmonary resuscitation.

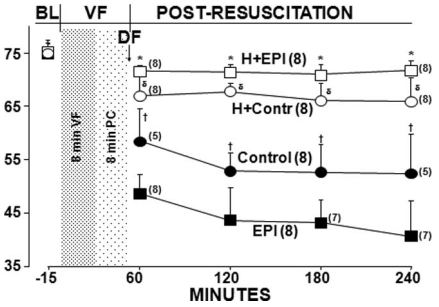

Figure 5. Ejection fraction, percentage. *$p <$ .05 vs. hypothermic control, normothermic control, and epinephrine. $^{\delta}p < .05$ vs. normothermic control and epinephrine. $^{\dagger}p < .05$ vs. normothermic epinephrine. *Control* in *closed circle*, normothermic control group; *EPI* in *closed square*, normothermic epinephrine group; *H+Contr* in *open circle*, hypothermic control group; *H+EPI* in *open square*, hypothermic epinephrine group. *BL*, baseline; *VF*, ventricular fibrillation; *DF*, defibrillation; *PC*, precordial compression; −15, 15 mins before ventricular fibrillation was induced; *CPR*, cardiopulmonary resuscitation.

and epinephrine had significantly better neurologic deficit scores during the first 48 hrs after ROSC (Table 4).

At autopsy, no significant abnormalities were observed on gross examination. More specifically, no CPR intervention-related injuries were observed.

DISCUSSION

Results of the present study again demonstrated that in this rat model of cardiac arrest and resuscitation, the reversal of global myocardial ischemia after cardiac resuscitation is followed by myocardial dysfunction. Epinephrine, when administered during normothermic CPR, increases CPP to levels that favor successful resuscitation. However, it increases the severity of postresuscitation myocardial dysfunction and consequently reduces duration of postresuscitation survival. Most importantly, these results, to our knowledge, are first to demonstrate that in settings of cardiac arrest and CPR, administration of epinephrine during hypothermia does not compromise its vasopressor effects. Furthermore, its adverse effects on postresuscitation myocardial function and survival when administered during the normothermic condition no longer exist when it is administered at the blood temperature of 34°C.

Postresuscitation myocardial dysfunction has been recognized as a major issue bearing on the high mortality rate, in addition to the underlying cardiac and coronary artery diseases that lead to cardiac arrest. Preexisting heart conditions may be a major contributor to the severity of postresuscitation myocardial dysfunction (1). In the Brain Resuscitation Multicenter Clinical Trial I, 262 patients were successfully resuscitated. Approximately 70% of these patients died within the first 72 hrs. Arterial hypotension,

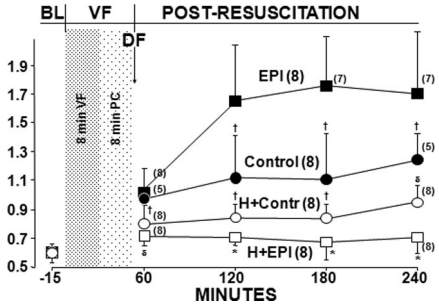

Figure 6. Myocardial performance index. *$p <$ .05 vs. hypothermic control, normothermic control, and epinephrine. $^{\delta}p < .05$ vs. normothermic control and epinephrine. $^{\dagger}p < .05$ vs. normothermic epinephrine. *Control* in *closed circle*, normothermic control group; *EPI* in *closed square*, normothermic epinephrine group; *H+Contr* in *open circle*, hypothermic control group; *H+EPI* in *open square*, hypothermic epinephrine group. *BL*, baseline; *VF*, ventricular fibrillation; *DF*, defibrillation; *PC*, precordial compression; −15, 15 mins before ventricular fibrillation was induced; *CPR*, cardiopulmonary resuscitation.

ventricular arrhythmias, and recurrent cardiac arrest were identified as the major causes of death (21). In multicenter clinical studies, 60% of 407 resuscitated patients died within 72 hrs. Arterial hypotension and ventricular arrhythmias were identified as predominant causes of death, and only 4.5% were ultimately discharged alive from the hospitals (4). In laboratory studies, we have previously demonstrated that the severity of postresuscitation myocardial dysfunction was related to the duration of cardiac arrest (8), the energy of electrical defibrillation (22, 23), and, most importantly, the β effects of epinephrine (8).

The mechanisms by which epinephrine administered during CPR increases the severity of postresuscitation myocardial dysfunction were initially shown by Ditchey and Lindenfeld (7). These investigators pointed to its β effects, by which the myocardial oxygen requirement was increased. During cardiac resuscitation in dogs, a bolus injection of 1 mg of epinephrine followed by continuous infusion of 0.2 mg/min over an interval of 10 mins increased myocardial lactate content and decreased myocardial ATP content even though coronary blood flow was doubled. The normal balance of myocardial energy supply and demand is disrupted during VF, because the demand of the myocardium for energy exceeds that which is available from the reserve of high-energy phosphates and from anaerobic glycolysis. The β-inotropic and -chronotropic effects of epi-

Table 2. Postresuscitation ST-segment elevation (in mV)

	60 mins, Mean ± SD	120 mins, Mean ± SD	240 mins, Mean ± SD
Normothermic control	0.05 ± 0.01	0.06 ± 0.01[a]	0.06 ± 0.01[a]
Normothermic epinephrine	0.06 ± 0.01	0.08 ± 0.01	0.08 ± 0.02
Hypothermic control	0.05 ± 0.01	0.06 ± 0.01[a]	0.05 ± 0.01[b]
Hypothermic epinephrine	0.01 ± 0.01[c]	0.035 ± 0.02[c]	0.034 ± 0.01[c]

[a]$p<.05$ vs. normothermic epinephrine; [b]$p<.05$ vs. normothermic control and epinephrine; [c]$p<.05$ vs. hypothermic control, normothermic control, and epinephrine.

Table 3. Outcomes of survival

	Return of Spontaneous Circulation	72 hrs	1 wk	1 mo	3 mos
Normothermic control, n	5/8	1/8	1/8	0/8	0/8
Normothermic epinephrine, n	8/8	1/8	1/8	1/8	1/8
Hypothermic control, n	8/8	8/8[a]	8/8[a]	7/8[a]	6/8[a]
Hypothermic epinephrine, n	8/8	8/8[a]	8/8[a]	8/8[a]	8/8[a]

[a]$p<.05$ vs. normothermic control and epinephrine.

Table 4. Postresuscitation neurologic deficit scores

	24 hrs, Mean ± SD	48 hrs, Mean ± SD	72 hrs, Mean ± SD	7 days, Mean ± SD
Normothermic control	398 ± 141	399 ± 149	453 ± 134	500 ± 0
Normothermic epinephrine	442 ± 116	452 ± 136	451 ± 137	444 ± 159
Hypothermic control	119 ± 49[a]	70 ± 35[a]	43 ± 30[a]	18 ± 22[a]
Hypothermic epinephrine	58 ± 32[b]	34 ± 29[b]	24 ± 25[a]	6 ± 12[a]

[a]$p<.05$ vs. normothermic control and epinephrine; [b]$p<.05$ vs. hypothermic control, normothermic control, and epinephrine.

nephrine further increase the already excessive myocardial oxygen requirement of the fibrillating heart. Consequently, the severity of myocardial ischemia is increased. In our own pig and rat models of cardiac arrest and resuscitation, we have consistently observed that when the β effects of epinephrine were blocked, the severity of postresuscitation myocardial dysfunction was significantly reduced to the extent that was comparable to that of a selective α_2-agonist (8, 24, 25). In the present study, we have again demonstrated the detrimental effects of epinephrine when administered during normothermic CPR. The most severe postresuscitation myocardial dysfunction and the shortest duration of survival were observed in a group of animals that received epinephrine during normothermic CPR. The β-adrenergic effects of epinephrine also account for increases in ventricular ectopy and the recurrence of ventricular tachycardia and VF (8, 26).

Hypothermia reduces the metabolic rate, and oxygen consumption is reduced accordingly (27, 28). Each 1°C decrease in temperature reduces the cerebral metabolic rate by 6%–7% (29). In isolated, perfused hearts, hypothermia of 30°C during 120 mins of ischemia suppressed anaerobic metabolism during ischemia and significantly diminished the elevation of left ventricular end-diastolic pressure at the end of ischemia. Postischemic myocardial function, coronary flow, and oxygen consumption were preserved (30). In the present study, postresuscitation myocardial function was significantly better in animals treated with both hypothermia and epinephrine when compared with those treated with hypothermia alone. Furthermore, the detrimental effects of epinephrine administered during normothermia as previously demonstrated by us and others no longer existed in animals that received epinephrine during hypothermia. There may be factors other than reduced myocardial metabolism and oxygen consumption after hypothermia that contribute to these findings.

The effects of blood temperature on adrenergic receptors remain to be explored. Results of previous studies indicated that the heart may be unresponsive or minimally responsive to an adrenergic agonist during hypothermic CPR when the cooling temperature was below 30°C (31–33). In the present study, comparable increases in CPP after administration of epinephrine were observed in both the hypothermic and normothermic groups, which indicates that the sensitivity of the α-adrenergic receptors was not altered when the blood temperature was reduced to 34°C. However, the reduced heart rate and incidence of recurrent VF immediately after successful resuscitation, which significantly improved postresuscitation myocardial function, and the duration of survival observed in animals treated with hypothermia and epinephrine suggest that the β-adrenergic effects of epinephrine were diminished at this temperature level. The selectively reduced β effects of epinephrine may not be related to the potential changes in catecholamine clearance with hypothermia. Our findings are consistent with those of Zellner et al (34), who demonstrated that hypothermia reduces the response of pig myocytes to β-adrenergic receptor stimulation.

Finally, we acknowledge the limitations of the present study. In contrast with human studies, this work was performed on another species, namely, mature male rats. The experimental animals were free from heart disease and anesthetized with pentobarbital.

CONCLUSIONS

Results of the present study demonstrated that therapeutic, mild hypothermia during CPR minimized the detrimental β effects of epinephrine. When epinephrine is administered during hypothermic CPR, it improves resuscitation, decreases the severity of postresuscitation myocardial and neurologic dysfunctions, and ultimately improves long-term survival rates when compared with epinephrine administered during CPR without hypothermia.

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