EXPERIMENTAL STUDIES

Alpha-Methylnorepinephrine, a Selective Alpha$_2$-Adrenergic Agonist for Cardiac Resuscitation

Shijie Sun, MD,*† Max Harry Weil, MD, PHD, FACC,*† Wanchun Tang, MD,*†
Takashi Kamohara, MD,* Kada Klouche, MD*

Palm Springs and Los Angeles, California

OBJECTIVES	The purpose of this study was to investigate the effects of a selective alpha$_2$-adrenergic agonist, alpha-methylnorepinephrine (alphaMNE) as an alternative vasopressor agent during cardiopulmonary resuscitation (CPR).
BACKGROUND	For more than 40 years, epinephrine has been the vasopressor agent of choice for CPR. Its beta- and alpha$_1$-adrenergic effects increase myocardial oxygen consumption, magnify global myocardial ischemia and increase the severity of postresuscitation myocardial dysfunction.
METHODS	Ventricular fibrillation (VF) was induced in 20 Sprague-Dawley rats. After 8 min of untreated VF, mechanical ventilation and precordial compression began. AlphaMNE, epinephrine or saline placebo was injected into the right atrium 2 min after the start of precordial compression. As an additional control, one group of animals was pretreated with alpha$_2$-receptor blocker, yohimbine, before injection of alphaMNE. Defibrillation was attempted 4 min later. Left ventricular pressure, dP/dt$_{40}$, negative dP/dt and cardiac index were measured for an interval of 240 min after resuscitation.
RESULTS	Except for saline placebo and yohimbine-treated animals, comparable increases in coronary perfusion pressure were observed after each drug intervention. All animals were successfully resuscitated. Left ventricular diastolic pressure, cardiac index, dP/dt$_{40}$ and negative dP/dt were more optimal after alphaMNE; this was associated with significantly better postresuscitation survival. Pretreatment with yohimbine abolished the beneficial effects of alphaMNE.
CONCLUSIONS	The selective alpha$_2$-adrenergic agonist, alphaMNE, was as effective as epinephrine for initial cardiac resuscitation but provided strikingly better postresuscitation myocardial function and survival. (J Am Coll Cardiol 2001;37:951–6) © 2001 by the American College of Cardiology

Rapid restoration of threshold levels of coronary perfusion and, therefore, myocardial blood flow during cardiopulmonary resuscitation (CPR) has been the overriding determinant of successful restoration of spontaneous circulation. Adrenergic vasopressor agents are employed to increase peripheral vascular resistance such as to increase aortic diastolic pressure and, consequently, coronary perfusion pressure and myocardial blood flow (1,2). The success of electrical defibrillation is contingent on restoring threshold levels of myocardial blood flow, especially when the duration of cardiac arrest is prolonged (3). Epinephrine, which has both alpha- and beta-adrenergic effects, enhances coronary perfusion during CPR. However, the beta- and, to a lesser extent, the alpha$_1$-adrenergic inotropic and chronotropic actions increase oxygen consumption of the fibrillating ventricles. Consistent with the historically important report by Redding et al. (4), current evidence suggests that these increases in oxygen demand before and during resuscitation are not compensated for by concurrent increases in

myocardial blood flow (5). Accordingly, epinephrine increases the severity of myocardial ischemia during CPR. Increases in unmet oxygen demands are likely to account for greater postresuscitation myocardial dysfunction and decreased postresuscitation survival after restoration of spontaneous circulation (2,6). We hypothesized that a selective alpha$_2$-adrenergic agonist would likely be a better vasopressor agent in settings of CPR. Activation of both beta- and alpha$_1$-adrenergic receptors in the myocardium account for both inotropic and chronotropic actions (7). This contrasts with alpha$_2$-agonists for which no receptors have been identified in the myocardium (8). In this study, the effects of a selective alpha$_2$-adrenergic agonist administered during CPR were compared with epinephrine with respect to initial resuscitation, postresuscitation myocardial function and postresuscitation survival after prolonged cardiac arrest. We also sought to validate our hypothesis by blocking the effects of the selective alpha$_2$-agonist with yohimbine.

METHODS

The protocol was approved by the Institutional Animal Care and Use Committee. All animals received humane care in compliance with the principles of laboratory animal care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources

Abbreviations and Acronyms	
alphaMNE	= alpha-methylnorepinephrine
CPR	= cardiopulmonary resuscitation
dP/dt$_{40}$	= measured at an intraventricular pressure of 40 mm Hg
FiO$_2$	= inspired oxygen fraction
PCO$_2$	= blood carbon dioxide tension
P$_{ET}$CO$_2$	= end tidal PCO$_2$
VF	= ventricular fibrillation

Figure 1. Experimental procedures. DF = defibrillation; Drug = either alphaMNE, epinephrine or saline placebo; FiO$_2$ = inspired oxygen fraction; MV = mechanical ventilation; PC = precordial compression; VF = ventricular fibrillation. *For alpha$_2$-receptor block (only in the group of animals which received alpha-methylnorepinephrine during cardiopulmonary resuscitation).

and published by the National Institutes of Health (NIH publication 86-32, revised 1996).

Animal preparation. Twenty male Sprague-Dawley rats weighing 450 to 550 g were fasted overnight except for free access to water. The animals were anesthetized by an intraperitoneal injection of 45 mg/kg pentobarbital sodium. Additional doses of 10 mg/kg were administered at hourly intervals but not within 30 min preceding onset of cardiac arrest. The trachea was orally intubated with a 14 g cannula mounted on a blunt needle (Abbocath-T, Abbott Hospital Inc., North Chicago, Illinois) with a 145° angled tip as previously described (2,6,9). End tidal blood carbon dioxide tension (P$_{ET}$CO$_2$) was measured with a side-stream infrared CO$_2$ analyzer (model 200, Instrumentation Laboratories, Lexington, Massachusetts) interposed between the tracheal cannula and the respirator. For measurement of left ventricular pressure, measured at an intraventricular pressure of 40 mm Hg (dP/dt$_{40}$) and negative dP/dt, a 23-gauge polyethylene catheter (Intramedic PE 50, Becton Dickinson, Sparks, Maryland) was advanced from the right carotid artery into the left ventricle. A 23-gauge polyethylene catheter (PE 50, Becton Dickinson, Sparks, Maryland) was advanced through the left external jugular vein, through the superior vena cava and into the right atrium. Intracardiac pressures were measured with reference to the midchest with a high sensitivity pressure transducer (model 42584-01, Abbott Critical Care System, North Chicago, Illinois). A 4F polyethylene catheter (model C-PMS-401J, Cook Critical Care, Bloomington, Indiana) was advanced through the right external jugular vein into the right atrium. A precurved guidewire supplied with the catheter was then advanced through the catheter into the right ventricle until an endocardial electrogram was confirmed. A 23-gauge polyethylene catheter (PE 50, Becton Dickinson, Sparks, Maryland) was advanced through the left femoral artery into the thoracic aorta for measurement of aortic pressure with a high sensitivity pressure transducer (model 42584-01, Abbott Critical Care System, North Chicago, Illinois). A thermocouple microprobe, 10 cm in length and 0.5 mm in diameter (9030-12-D-34, Columbus Instruments, Columbus, Ohio), was advanced from the right femoral artery into the descending thoracic aorta. Blood temperature was measured with this sensor. A 23-gauge polyethylene catheter (PE 50, Becton Dickinson, Sparks, Maryland) was advanced through the right femoral vein into the inferior vena cava for sampling venous blood and for blood transfusion. The electrocardiogram lead II was continuously recorded.
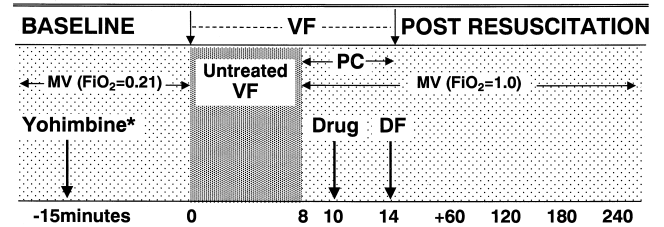
Experimental procedure. The experimental protocol is summarized in Figure 1. Fifteen minutes before inducing ventricular fibrillation (VF), the animals were randomized by the sealed envelope method as previously described (6). The investigators were blinded to each intervention. For animals randomized to receive the selective alpha$_2$-adrenergic receptor blocking agent, yohimbine, a dose of 100 μg/kg was injected into the right atrium 15 min before inducing VF. Ventricular fibrillation was induced with a 60 cycle alternating current of 3 mA delivered to the right ventricular endocardium. The current flow was continued for 3 min to sustain VF (2,6,9). Mechanical ventilation was discontinued after onset of VF. Precordial compression was begun 8 min after onset of VF with a pneumatically driven mechanical chest compressor as previously described (2,6,9). Coincident with the start of precordial compression, the animal was mechanically ventilated. Tidal volume was established at 0.65 ml/100 g animal weight, a frequency of 100/min and with an inspired oxygen fraction (FiO$_2$) of 1.0. Precordial compression at a rate of 200 min^{-1} was synchronized to provide a compression/ventilation ratio of 2:1 with an equal compression-relaxation duration. Depth of compression was adjusted to maintain the coronary perfusion pressure at 23 ± 2 mm Hg. This typically yielded a P$_{ET}$CO$_2$ of 11 ± 2 mm Hg. Either 100 μg/kg of alpha-methylnorepinephrine (alphaMNE), 30 μg/kg of epinephrine or saline placebo was injected into the right atrium over a 10 s interval beginning 2 min after the start of precordial compressions. Resuscitation was attempted with up to three, 2 J countershocks after 14 min of cardiac arrest and 6 min after the start of precordial compression. Restoration of spontaneous circulation was defined as the return of supraventricular rhythm with a mean aortic pressure of 60 mm Hg for a minimum of 5 min. Mechanical ventilation with an FiO$_2$ 1.0 was continued for 4 h after successful resuscitation. All catheters, including the endotracheal tube, were then removed. The animals were observed for an additional 68 h after which they were euthanized with an intraperitoneal injection of pentobarbital. At autopsy, organs were inspected for gross abnormalities, including
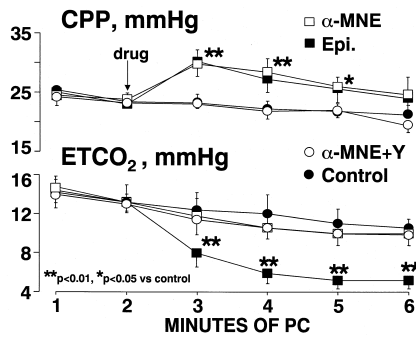
Figure 2. Effects of four interventions on CPP and $ETCO_2$ during precordial compression. Values are mean ± standard deviation. αMNE = alpha-methylnorepinephrine; αMNE+Y = alpha-methylnorepinephrine pretreated with yohimbine; CPP = coronary perfusion pressure; drug = the time of administration of the drugs; Epi. = epinephrine; $ETCO_2$ = end tidal PCO_2; PC = precordial compression. *p < 0.05; **p < 0.01.

evidence of traumatic injury consequent to cannulation, airway management or precordial compression.

Measurements. Aortic, left ventricular and right atrial pressures, electrocardiogram and $P_{ET}CO_2$ were continuously recorded on a PC-based data acquisition system supported by CODAS software (DATAQ Inc, Akron, Ohio). Coronary perfusion pressure was calculated as the difference between decompression diastolic aortic and time-coincident right atrial pressure measured at the end of each minute of precordial compression. A 1.0-ml aliquot of arterial blood from a donor rat of the same colony was transfused into the inferior vena cava immediately after withdrawal of 0.5-ml samples from the aortic and from the inferior vena cava catheter. Blood oxygen tension, blood carbon dioxide tension (PCO_2) and lactic acid were measured on these samples by techniques previously described (2,6,9). At 5 min after the start of precordial compression and at 120 and 240 min after successful resuscitation, this panel of measurements was repeated. Myocardial function was assessed from measurements of left ventricular pressures and cardiac output. The rate of left ventricular pressure increase was measured by analog differentiation of left ventricular pressure at 40 mm Hg (dP/dt_{40}) for quantitation of isovolemic contractility. The rate of maximal left ventricular pressure decline ($-dP/dt$) was measured as an estimate of myocardial relaxation (2,6,9). Cardiac output was measured by a thermodilution technique in which a bolus of 200 μl of saline at a temperature of 12°C was injected into the right atrium. Duplicate thermodilution curves were

obtained with the aid of a cardiac output computer fabricated by our institute. Duplicate measurements in each instance differed by 5%.

Statistical analyses. For measurements between groups, analysis of variance and Scheffe's multicomparison techniques were used. Comparisons between time-based measurements within each group were performed with analysis of variance repeated measurements. The outcome differences were analyzed with Fisher exact test. Measurements are reported as mean ± standard deviation. A value of p < 0.05 was considered significant.

RESULTS

Baseline hemodynamic and blood analytical measurements did not differ significantly among the four groups. There were no differences in aortic pressure and blood gas measurements between groups during CPR and after successful resuscitation. After administration of alphaMNE, coronary perfusion pressure was increased from 24 ± 1 to 30 ± 2 mm Hg (p < 0.01). Comparable increases in coronary perfusion pressure from 23 ± 1 to 30 ± 3 mm Hg (p < 0.01) were observed with epinephrine. In animals pretreated with yohimbine, no increases in coronary perfusion pressure followed administration of alphaMNE (Fig. 2). Though comparable increases in coronary perfusion pressure were observed after both alphaMNE and epinephrine, $P_{ET}CO_2$ was unaffected by alphaMNE, but it was significantly decreased after epinephrine (Fig. 2). All animals were successfully resuscitated after electrical defibrillation. The number of electrical shocks required for restoration of spontaneous circulation was significantly greater in placebo-treated animals (p < 0.01) and epinephrine-treated animals (p < 0.05) compared to animals treated with alphaMNE. The total number of postresuscitation ventricular ectopic beats during the first 10 min after successful resuscitation was significantly greater in both placebo-treated and epinephrine-treated animals (Table 1). As we previously observed, dP/dt_{40} was significantly decreased in all animals after successful resuscitation (2,6). Decreased contractility was associated with a significant decrease in cardiac index (Fig. 3 and 4). However, alphaMNE significantly reduced the severity of myocardial contractile dysfunction. This contrasted with animals treated with epinephrine or with saline placebo in which there was greater impairment of myocardial contractility. After alphaMNE, we also observed

Table 1. Effects of Treatment on Number of Defibrillation, Postresuscitation Ventricular Arrhythmias and Duration of Survival

Treatment	Number of Defibrillations	PVCs	Survival (h)
Alpha-methylnorepinephrine	1.6 ± 0.9†‖	287 ± 342*§	72 ± 0†‖
Alpha-methylnorepinephrine with yohimbine	3.0 ± 0.7‡§	687 ± 642	20 ± 7
Epinephrine	3.8 ± 1.9	1,097 ± 816	19 ± 8
Control	4.9 ± 0.8	1,054 ± 605	16 ± 4

*p < 0.05; †p < 0.01 vs. epinephrine; ‡p < 0.05 vs. alpha-methylnorepinephrine; §p < 0.05; ‖p < 0.01 vs. control.
   PVCs = ventricular ectopic beats during the first 10 min after resuscitation.
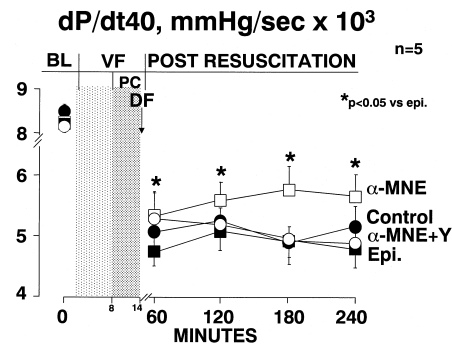
Figure 3. Effects of four interventions on postresuscitation dP/dt$_{40}$. Values are mean $\pm$ standard deviation. αMNE = alpha-methylnorepinephrine; αMNE+Y = alpha-methylnorepinephrine pretreated with yohimbine; BL = baseline; DF = defibrillation; Epi. = epinephrine; PC = precordial compression; VF = ventricular fibrillation. *p < 0.05 vs. epinephrine.
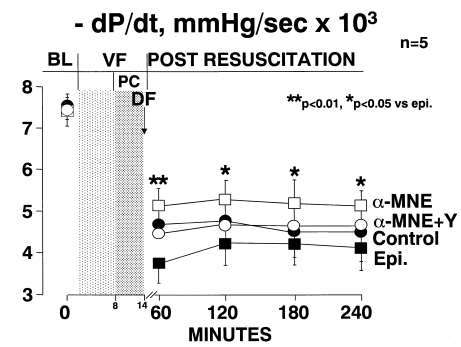
Figure 5. Effects of four interventions on postresuscitation −dP/dt. Values are mean $\pm$ standard deviation. αMNE = alpha-methylnorepinephrine; αMNE+Y = alpha-methylnorepinephrine pretreated with yohimbine; BL = baseline; DF = defibrillation; Epi. = epinephrine; PC = precordial compression; VF = ventricular fibrillation. *p < 0.05; **p < 0.01 vs. epinephrine.

improvement in −dP/dt and, therefore, myocardial relaxation (Fig. 5) together with left ventricular end diastolic pressure (Fig. 6). These myocardial protective effects of alphaMNE were fully blocked by pretreatment with yohimbine. Finally, the duration of postresuscitation survival was also significantly improved after alphaMNE. Each animal treated with alphaMNE survived for more than 72 h. This contrasted with epinephrine-treated animals, which survived for an average of 19 h, and placebo controls, which survived for an average of 16 h (Table 1). These beneficial effects of alphaMNE on postresuscitation survival were also blocked by yohimbine.

DISCUSSION

Like epinephrine, alphaMNE increases coronary perfusion pressure to levels that favor successful resuscitation in our animal model. However, electrical defibrillation was achieved with greater ease and with significantly less total electrical energies after treatment with alphaMNE. End tidal PCO$_2$ remained unchanged after alphaMNE, which indicated that, unlike epinephrine, this selective alpha$_2$-adrenergic agent does not produce pulmonary ventilation/perfusion defects (10). After successful resuscitation, the

incidence of postresuscitation ventricular arrhythmias was strikingly reduced after administration of alphaMNE, and there was a highly significant reduction in postresuscitation myocardial dysfunction in animals treated with alphaMNE. These beneficial effects were associated with a significantly increased duration of postresuscitation survival. Pretreatment with yohimbine abolished these beneficial effects, confirming our hypothesis that selective alpha$_2$-adrenergic receptor activation provided a better option than epinephrine. There is a slight likelihood of successful cardiac resuscitation without reestablishment of threshold levels of coronary perfusion, especially if the duration of cardiac arrest is prolonged. Since coronary and cerebral circulation is directly related to the arterial pressures generated, vasoconstrictor agents serve to increase peripheral vascular resistance and, thereby, preferentially increase coronary and cerebral blood flows. This is the rationale for the routine use of vasopressor agents during CPR (11).

Potential limitations of epinephrine during CPR. Epinephrine has been the preferred adrenergic amine for the treatment of human cardiac arrest for almost 40 years (1,12–14). However, epinephrine has potent effects on both
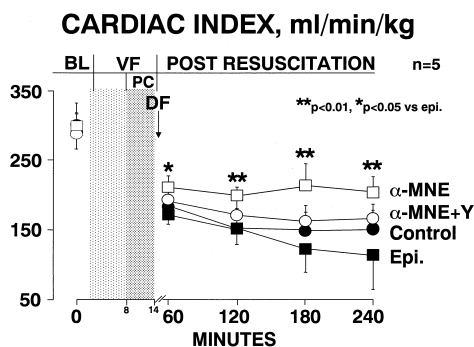
Figure 4. Effects of four interventions on postresuscitation cardiac index. Values are mean $\pm$ standard deviation. αMNE = alpha-methylnorepinephrine; αMNE+Y = alpha-methylnorepinephrine pretreated with yohimbine; BL = baseline; DF = defibrillation; Epi. = epinephrine; PC = precordial compression; VF = ventricular fibrillation. *p < 0.05; **p < 0.01 vs. epinephrine.
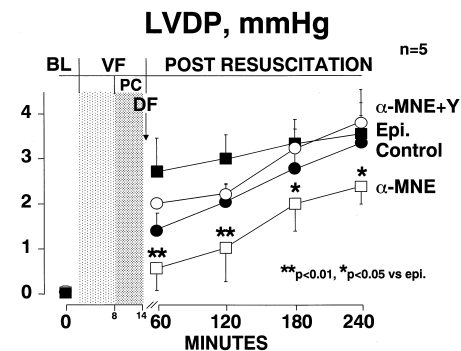
Figure 6. Effects of four interventions on postresuscitation LVDP. Values are mean $\pm$ standard deviation. αMNE = alpha-methylnorepinephrine; αMNE+Y = alpha-methylnorepinephrine pretreated with yohimbine; BL = baseline; DF = defibrillation; Epi. = epinephrine; LVDP = left ventricular end-diastolic pressure; PC = precordial compression; VF = ventricular fibrillation. *p < 0.05; **p < 0.01 vs. epinephrine.

Table 2. Adrenergic Receptors Actions on the Heart and Peripheral Arteries

Receptors	Heart	Peripheral Arterial Vascular
Alpha$_1$	↑ Contractility	Constriction
Alpha$_2$	↑ MVO$_2$	
Central	Bradycardia	Dilation
Peripheral	—	Constriction
Beta$_1$	↑ ↑ Contractility	—
	↑ MVO$_2$	
Beta$_2$	↑ Contractility	Dilation
	↑ MVO$_2$	

MVO$_2$ = myocardial oxygen consumption.

alpha- and beta-receptors, including alpha$_1$-, alpha$_2$- and beta$_1$- and beta$_2$-receptors (Table 2). The beta$_1$- and beta$_2$-adrenergic actions are inotropic and chronotropic and, thereby, increase the already excessive myocardial oxygen requirements of the fibrillating heart. These increases in oxygen demand fail to be fulfilled by the very limited blood flow generated by precordial compression, which is only between 25% to 30% of resting physiological levels (6). Accordingly, epinephrine produces vasoconstriction and, thereby, increases coronary perfusion pressure during CPR. However, postresuscitation myocardial function and survival decreases as a consequence of the greater severity of global myocardial ischemia (2).

Potential limitations of selective alpha$_1$-adrenergic agonists during CPR. Activation of alpha-adrenergic receptors account for the increases in peripheral vascular resistance and consequent increases in both myocardial and cerebral perfusion pressure and blood flow. However, we now recognize that there is a rapid desensitization of alpha$_1$-adrenergic receptors when the myocardium becomes ischemic (15,16). This is consistent with earlier observations, which indicated that predominant alpha$_1$-agonists, including methoxamine and phenylephrine, are less effective than epinephrine after prolonged cardiac arrest (17). In addition, it is now apparent that stimulation of myocardial alpha$_1$-adrenergic receptors increases both inotropic and chronotropic responses, myocardial oxygen consumption and, thereby, augments global ischemic injury (18). When alpha$_1$-adrenergic receptors are blocked by either a selective or nonselective alpha-adrenergic blocker, myocardial function is significantly improved after acute myocardial infarction (19). In addition, alpha$_1$-adrenergic agonists constrict coronary arteries such that there is further reduction in myocardial blood flow (20).

Rationale for the use of selective alpha$_2$-adrenergic agonists during CPR. Stimulation of postsynaptic alpha$_2$-adrenergic receptors produces systemic vasoconstriction without concurrent increases in myocardial oxygen requirement (21). Contrasted with alpha$_1$-adrenergic receptors, stimulation of postsynaptic alpha$_2$-adrenergic receptors increases endothelial nitric oxide production, which counterbalances alpha$_2$-adrenergic stimulation induced coronary vasoconstriction (19). Stimulation of presynaptic alpha$_2$-adrenergic receptors inhibits the release of endogenous catecholamines. This is likely to be beneficial since greater levels of endogenous catecholamines during CPR were associated with poor outcomes (22). These considerations prompted the concept that selective alpha$_2$-adrenergic agonists may be more optimal vasopressor agents in settings of cardiac arrest. The rationale for the use of a selective alpha$_2$-adrenergic agonist is also supported by experimental studies on regional myocardial ischemia. Clonidine, an alpha$_2$-adrenergic agonist, decreased the severity of postischemic myocardial dysfunction after 10 min of left anterior descending coronary artery occlusion (23). Perioperative administration of selective alpha$_2$-adrenergic agonists, including clonidine and mivazerol, reduced the severity of myocardial ischemia in settings of coronary artery disease (24,25). A major limitation of currently available selective alpha$_2$-adrenergic agonists, including clonidine, is the ease with which these drugs cross the blood-brain barrier, especially when the function of this barrier is decreased during ischemia (26). In the central nervous system, alpha$_2$-adrenergic agonists exert a negative inotropic and chronotropic action (27). Accordingly, there is a decline in myocardial contractility and arterial pressure. This prompted the introduction of alpha$_2$-agonists for the treatment of hypertension, recognizing the risk of initial hypertension due to its peripheral action. Alpha-methylnorepinephrine, however, had no such negative inotropic and chronotropic effects after resuscitation in the present model, consistent with earlier findings that this agent does not cross the blood-brain barrier (28,29).

Study limitations. In contrast with settings of human cardiac arrest, experiments were performed on another species, namely, mature male rats. The experimental animals were free of heart disease and anesthetized with pentobarbital.

CONCLUSIONS

We conclude that the administration of the selective alpha$_2$-adrenergic agonist, alphaMNE, significantly improves the outcome of CPR when compared with epinephrine and that such improvement is associated with lesser postresuscitation ventricular arrhythmias and better postresuscitation myocardial function.

Reprint requests and correspondence: Dr. Max Harry Weil, The Institute of Critical Care Medicine, 1695 North Sunrise Way, Building #3, Palm Springs, California 92262-5309. E-mail: weilm@aol.com.

REFERENCES

1. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. II. Adult basic life support. III. Adult advanced life support. JAMA 1992;268:2184–241.
2. Tang W, Weil MH, Sun SJ, Noc M, Yang L, Gazmuri RJ. Epinephrine increases the severity of postresuscitation myocardial dysfunction. Circulation 1995;92:3089–93.

3. Tang W, Weil MH, Sun SJ, et al. The effects of biphasic and conventional monophasic defibrillation on postresuscitation myocardial function. J Am Coll Cardiol 1999;4:815–22.

4. Redding JS, Pearson JW. Evaluation of drugs for cardiac resuscitation. Anesthesiology 1963;24:203–7.

5. Ditchey RV, Lindenfeld J. Failure of epinephrine to improve the balance between myocardial oxygen supply and demand during closed-chest resuscitation in dogs. Circulation 1988;78:382–9.

6. Sun SJ, Weil MH, Tang W, Povoas HP, Mason E. Combined effects of buffer and adrenergic agents on postresuscitation myocardial function. J Pharm Exp Ther 1999;291:773–7.

7. Broadley KJ, Williamson KL, Roach AG. In vivo demonstration of alpha-adrenoceptor-mediated positive inotropy in pithed rats: evidence that adrenaline does not stimulate myocardial alpha-adrenoceptors. J Auton Pharmacol 1999;19:55–63.

8. Lefkowitz RJ. Neurotransmission. The autonomic and somatic motor nervous system. In: Goodman LS, Gilman A, editors. The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill, 1996:125.

9. Sun SJ, Weil MH, Tang W, Fukui M. Effects of buffer agents on postresuscitation myocardial dysfunction. Crit Care Med 1996;24:2035–41.

10. Tang W, Weil MH, Gazmuri RJ, Sun SJ, Duggal C, Bisera J. Pulmonary ventilation/perfusion defects induced by epinephrine during cardiopulmonary resuscitation. Circulation 1991;84:2101–7.

11. Weil MH, Tang W. Cardiopulmonary resuscitation: a promise that is as yet largely unfulfilled. Dis Mon 1997;43:429–504.

12. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency care (ECC). JAMA 1974;227 Suppl:833–68.

13. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency care (ECC). JAMA 1980;240:453–509.

14. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency care (ECC). JAMA 1986;255:2905–89.

15. Dillon JS, Gu XH, Nayler WG. Alpha-1 adrenoceptors in the ischemic and reperfused myocardium. J Mol Cell Cardiol 1988;20:725–35.

16. Zhao M, Hagler HK, Muntz KH. Regulation of alpha 1-, beta 1- and beta 2-adrenergic receptors in rat heart by norepinephrine. Am J Physiol 1996;271:H1762–8.

17. Brown CG, Birinyi F, Werman HA, Davis EA, Hamlin RL. The comparative effects of epinephrine versus phenylephrine on regional cerebral blood flow during cardiopulmonary resuscitation. Resuscitation 1986;14:171–83.

18. Grupp IL, Lorenz JN, Walsh RA, Boivin GP, Rindt H. Overexpression of alpha 1B-adrenergic receptor induces left ventricular dysfunction in the absence of hypertrophy. Am J Physiol 1998;275:H1338–50.

19. Gregorini L, Marco J, Kozakova M, et al. Alpha-adrenergic blockade improves recovery of myocardial perfusion and function after coronary stenting in patients with acute myocardial infarction. Circulation 1999;99:482–90.

20. Ishibashi Y, Duncker DJ, Bache RJ. Endogenous nitric oxide masks alpha 2-adrenergic coronary vasoconstriction during exercise in the ischemic heart. Circ Res 1997;80:196–207.

21. Brodde OE. Physiology and pharmacology of cardiovascular catecholamine receptors: implications for treatment of chronic heart failure. Am Heart J 1990;120:1565–72.

22. Lindner KH, Haak T, Keller A, Bothner U, Lurie KG. Release of endogenous vasopressors during and after cardiopulmonary resuscitation. Br Heart J 1996;75:145–50.

23. Meissner A, Weber TP, Van Aken H, Zbieranek K, Rolf N. Clonidine improves recovery from myocardial stunning in conscious chronically instrumented dogs. Anesth Analg 1998;87:1009–14.

24. Stuhmeier KD, Mainzer B, Cierpka J, Sandmann W, Tarnow J. Small oral dose of clonidine reduces the incidence of intraoperative myocardial ischemia in patients having vascular surgery. Anesthesiology 1996;85:706–12.

25. McSPI-Europe Research Group. Perioperative sympatholysis: beneficial effects of the alpha 2-adrenoceptor agonist mivazerol on hemodynamic stability and myocardial ischemia. Anesthesiology 1997;86:346–63.

26. Shinnou M, Ueno M, Sakamoto H, Ide M. Blood-brain barrier damage in reperfusion following ischemia in the hippocampus of the mongolian gerbil brain. Acta Neurol Scand 1998;98:406–11.

27. Kahn ZP, Ferguson CN, Jones RM. Alpha-2 and imadazoline receptor agonists: their pharmacology and therapeutic role. Anesthesia 1999;54:146–65.

28. Ruffolo RR, Jr, Nichols AJ, Stadel JM, Hieble JP. Pharmacologic and therapeutic applications of alpha$_2$-adrenoceptor subtypes. Annu Rev Pharmacol Toxicol 1993;32:243–79.

29. Schäfers RF, Nürnberger J, Herrmann B, et al. Adrenoceptors mediating the cardiovascular and metabolic effects of a-methylnoradrenaline in humans. J Pharmacol Exp Ther 1999;289:918–25.