Controversial issues in drug treatment during cardiopulmonary resuscitation

Deborah R. Van Pelt, DVM, MS, and Wayne E. Wingfield, DVM, MS

The advent of modern cardiopulmonary resuscitation (CPR) began in 1960 with the description of external thoracic compressions and, until recently, many of the theories and techniques of CPR were not questioned.[1] Recent studies have brought forth new information challenging some of these long-standing but unproven theories about cardiopulmonary arrest and its successful management.[1] The goal of CPR is to restore and maximize coronary and cerebral perfusion with oxygenated blood by restoring normal cardiac rhythm, concomitant with providing effective respiratory exchange and hemodynamic support; achieving this goal involves use of various types of drugs as well as the IV administration of fluids. The selection of appropriate drugs to meet the goals of CPR, as well as the quantity of fluids to be administered, remain important and somewhat controversial issues in both human and veterinary CPR. This report deals with some of the key controversial issues of drug treatment in managing cardiopulmonary arrest.

Methods to Improve Blood Flow

Adequate oxygen delivery to the brain and myocardium is crucial to the success of CPR. Myocardial oxygen delivery is dependent on arterial oxygen content (Ca_{O_2}) and myocardial blood flow; myocardial blood flow can be calculated as the difference between aortic diastolic pressure and right atrial diastolic pressure, divided by myocardial vascular resistance.[2] Cerebral perfusion pressure is dependent on cardiac output and cerebral vascular resistance.[3] Increasing myocardial and cerebral oxygen delivery therefore requires maximizing Ca_{O_2}, cardiac output, and aortic diastolic pressure, while minimizing right atrial diastolic pressure and coronary and cerebral vascular resistances. Optimizing Ca_{O_2} is accomplished by administration of 100% oxygen and by assuring adequate hemoglobin concentrations, which may require RBC transfusion.

From the Department of Clinical Sciences and Veterinary Teaching Hospital, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523.

Address reprint requests to Dr. Wingfield.

To facilitate forward blood flow during CPR, IV administration of fluids to achieve volume loading obviously would seem appropriate. Because IV administration of fluids has been demonstrated to increase carotid artery blood flow and, in some cases, the arterial pressure generated by external thoracic compression,[4] it further seems reasonable that volume expansion should increase forward blood flow and therefore improve the success of CPR. Recently, however, this theory has come into question, because a positive correlation between coronary perfusion pressure and success of resuscitation has been documented.[2,5] To increase coronary perfusion pressure, the gradient between aortic and right atrial diastolic pressures must increase, by increasing aortic pressure or decreasing right atrial pressure. An investigation into the potential adverse effects of volume loading during closed-thorax CPR in dogs revealed that rapid administration of 1 L of 0.9% saline solution or 10% dextran in dogs weighing 20 to 50 kg substantially increased total forward blood flow.[2] However, blood flow to the cerebral hemispheres, cerebellum, brainstem, and ventricular myocardium decreased.[2] These deleterious changes in critical regional flows were accompanied by disproportionate increases in right atrial and intracranial pressures, relative to the increase in aortic pressure, which reduced the pressure gradient across the coronary and cerebral circulations. These changes in blood flow were thought to be influenced somewhat by a decrease in systemic vascular resistance. Volume expansion may have had different effects on regional blood flow during CPR if vascular resistance had been supported pharmacologically. On the basis of these findings, however, fluid administration during CPR should be conservative, unless intravascular volume depletion is a contributing cause to cardiac arrest.

Administration of adrenergic agonists during CPR also is aimed at improving blood flow. α-Adrenergic receptors subserve vasoconstriction in peripheral arterial vasculature, whereas β_2-adrenergic receptors subserve arterial vasodilatation. α-Adrenergic agonists offer several beneficial circulatory effects during CPR, including peripheral

vasoconstriction, resulting in increased venous return to the heart; increased aortic diastolic pressure, resulting in increased coronary blood flow; and vasoconstriction of extracerebral portions of the carotid arteries, resulting in increased intracerebral blood flow.[1,6-8] Drugs with α-adrenergic activity include epinephrine, norepinephrine, phenylephrine, and methoxamine. Drugs with powerful β-adrenergic activity, such as epinephrine and isoproterenol, increase the vigor of ventricular fibrillation and have a positive inotropic effect.[1,6,8,9] Potential disadvantages of cardiac β-adrenergic stimulation include increased myocardial oxygen demand, increased incidence of dysrhythmias after return of spontaneous circulation, and increased heart rate, resulting in further increases in myocardial oxygen consumption after return of spontaneous circulation.[6,8]

Redding's study in 1963 revealed that early administration of epinephrine during CPR improved recovery rates, and this beneficial outcome was postulated to be attributable to increased aortic diastolic pressure with improved myocardial perfusion.[1] Numerous studies in human beings and animals have confirmed these findings.[1,6,7] Owing to its powerful α-adrenergic effects, epinephrine induces intense vasoconstriction that prevents substantial runoff in peripheral arteries, thus preventing arterial collapse and maintaining arterial pressure.[7] Epinephrine also increases aortic diastolic pressure without increasing right atrial pressure. The subsequent increase in coronary perfusion pressure may be as large as 25 to 30 mm of Hg when epinephrine administration is combined with simultaneous thoracic compression-ventilation CPR.[7,a]

Cerebral perfusion pressure also is reasonably preserved by the administration of epinephrine during resuscitation.[7,10,11] Cerebral oxygen delivery can be maintained without reaching maximal oxygen extraction, implying that oxygen delivery is greater than that necessary to maintain aerobic metabolism.[1,12] Epinephrine improves blood flow to the brain by preventing or reversing carotid artery collapse while causing vasoconstriction of the extracerebral portions of the carotid arteries, thereby increasing cerebral perfusion pressure.[7]

A study designed to determine the importance of α- and β-adrenergic receptors during resuscitation revealed that α-receptor stimulation, with concomitant increased aortic diastolic pressure, was more important to the success of resuscitation than was β-receptor stimulation.[6] In 10 dogs treated with the β-blocking agent propranolol before CPR and then given phenylephrine during resuscitation, as well as in 10 dogs given only epinephrine during resuscitation, 100% return of spontaneous circulation was found after 5 minutes of asphyxial arrest. However, of 11 dogs treated with the α-adrenergic blocker phenoxybenzamine before CPR and then administered isoproterenol, only 27% were resuscitated successfully. This study thus revealed that the primary usefulness of epinephrine in resuscitation was attributable to its α-adrenergic vasoconstrictor effects, rather than its effects as a cardiac β_1-receptor agonist.

The use of pure α agonists, therefore, may offer some promise in CPR. Numerous studies have been performed to determine the effectiveness of various α agonists, relative to that of epinephrine, in supporting cerebral and coronary blood flow.[10-16] In several studies comparing epinephrine with methoxamine, phenylephrine, and norepinephrine, significant differences in coronary blood flow, myocardial oxygen delivery, patient survival, or neurologic outcome were not demonstrated between epinephrine and the more selective α agonists.[9,12,15-17,b,c] In several studies of swine with cardiac arrest, however, cerebral blood flow was significantly greater with administration of epinephrine than with doses of methoxamine or phenylephrine that induced equivalent pressor effects.[10,11,18] This may be explained, in part, by the distribution of adrenergic receptors in the cerebral vasculature. Although α-receptor stimulation may be required to prevent arterial runoff and preserve aortic diastolic pressure, the cerebral microvasculature dilates in response to β_2-receptor stimulation.[10,11] Therefore, to allow perfusion of cerebral tissues, β_2-adrenergic stimulation may be advantageous. Because methoxamine and phenylephrine lack substantial β_2-adrenergic vasodilator activity, their selective α-adrenergic activity results in cerebral blood vessel constriction, with shunting of blood from the tissue.

In another study also involving swine in cardiac arrest,[13] treatment with epinephrine improved regional myocardial blood flow, increased coronary sinus oxygen content, and improved oxygen extraction ratio, when compared with phenylephrine. In 102 human patients who developed cardiac arrest caused by ventricular fibrillation before hospital admission, conversion rates (percentage of patients developing a pulse during resuscitation) and successful resuscitations (defined as the conveyance of a patient having a pulse to the emergency department) were significantly greater with epinephrine than with methoxamine.[14] Although the trend toward greater survival to discharge in this study was not reported as significant, most investigators agree that epinephrine is the adrenergic drug of choice in CPR, owing to its greater ability to improve cerebral and myocardial blood flows, relative to the effects of pure α agonists.[14]

Until recently, the dosage of epinephrine rec-

[a]Michael JR, Koehler RC, Guerci AD, et al. Epinephrine improves myocardial perfusion during cardiopulmonary resuscitation in dogs (abstr). *Anesthesiology* 1983;59:A122.

[b]Hoekstra JW, VanLigten PF, Neumar R, et al. Effect of high-dose norepinephrine versus epinephrine on cerebral and myocardial blood flow during CPR (abstr). *Ann Emerg Med* 1989;18:187.

ommended by the American Heart Association in human beings during CPR was 0.02 mg/kg of body weight, IV.[15,19] However, high-dose administration of epinephrine (0.2 mg/kg) has been shown to improve myocardial and cerebral blood flow, oxygen extraction, aortic-to-right atrial pressure gradient (and therefore, coronary perfusion pressure), and ease of resuscitation in human beings and animals in cardiac arrest.[1,10,11,13,20-24,d,e] In a study of 50 human patients, spontaneous circulation returned in 12% of 25 patients given the standard dose of epinephrine vs 36% of 25 patients administered the higher dose.[f] Significant effect was not seen on long-term survival. In another study of 49 adult human patients with nontraumatic cardiac arrest, 60% of patients receiving epinephrine at the high dose were resuscitated vs 15.4% of patients receiving the standard dose.[g] High-dose administration of epinephrine was significantly more effective than administration of standard doses in resuscitating patients with circulatory arrest from ventricular fibrillation and asystole (nonperfusing rhythms), but significant difference was not found in resuscitation rates between high and standard doses in patients with electromechanical dissociation (EMD) or ventricular tachycardia, in which some perfusion is maintained (perfusing rhythms). High-dose administration of epinephrine in pediatric and adult human patients with cardiac arrest that was refractory to standard doses of epinephrine has been shown to result in return of spontaneous circulation in 70 to 100% of these patients.[22,23]

Several investigators have questioned the use of high-dose treatment with epinephrine, emphasizing instead the potential problems of hyperglycemia, hyperkalemia, cardiac dysrhythmias, and myocardial necrosis. However, high-dose administration in swine did not increase the prevalence of dysrhythmias or cardiovascular instability, and may have had beneficial effects on mean arterial pressure and cardiac output after resuscitation.[h] Likewise, in human patients in whom administration of standard doses of epinephrine had been unsuccessful, high-dose administration of epinephrine established a perfusing rhythm without CNS, myocardial, or metabolic alterations secondary to treatment with the high dose.[23,i] These findings would appear to support the continued investigation of high-dose administration of epinephrine in cardiac arrest and its use in clinical cases refractory to the lower standard doses.

Drugs to Control Heart Rate and Rhythm

In human and animal patients with cardiac arrest, early recognition of the predominant dysrhythmia and prompt aggressive treatment offer improved chance of resuscitation and patient survival.[24] Three commonly occurring dysrhythmias during cardiac arrest in human beings and animals include ventricular fibrillation, asystole, and EMD.[d]

Success in the treatment of ventricular fibrillation is dependent on early direct-current defibrillation.[24] Clinical experience in human medicine has revealed that after 5 minutes of fibrillation, the success of electric defibrillation is greatly reduced.[j] If the ventricles have been fibrillating for > 4 minutes, administration of drugs such as epinephrine or methoxamine is recommended prior to electric defibrillation. Although several studies have failed to support the efficacy of epinephrine in the treatment of dogs with ventricular fibrillation,[15,17] a study of prehospitalization ventricular fibrillation in human beings showed a significantly greater percentage developing a pulse after epinephrine administration vs methoxamine administration, although no difference was found in survival rates.[14,15,17]

Other drugs frequently administered in the treatment of ventricular fibrillation include the antiarrhythmic agents lidocaine and bretylium tosylate. Lidocaine is a class-1b, membrane-stabilizing antidysrhythmic drug that decreases the velocity of cardiac impulse conduction by blocking rapid sodium movement into myocardial cells.[25] Lidocaine also suppresses ectopic automaticity, decreases tissue excitability, and may prolong the effective refractory period of injured or partially depolarized cells.[25] Lidocaine is administered to animals and human beings in ventricular fibrillation in attempts to accomplish chemical conversion to a perfusing rhythm; it is also administered prior to electric defibrillation with the goal of increasing the success of electric conversion. When administered to dogs immediately after CPR was begun, lidocaine (2 mg/kg, IV) has been demonstrated to significantly increase the threshold for the development of ventricular fibrillation within 5 minutes of administration; however, the response decreased as resus-

[c]Robinson LA, Brown CG, Jenkins J, et al. The effect of norepinephrine versus epinephrine on myocardial hemodynamics during CPR (abstr). *Ann Emerg Med* 1988;17:12.

[d]Paradis NA, Martin GB, Rivers EP, et al. High-dose epinephrine and coronary perfusion pressure during cardiac arrest in human beings (abstr). *Ann Emerg Med* 1989;18:478.

[e]Paradis NA, Goetting MG, Rivers EP, et al. High-dose epinephrine therapy and return of spontaneous circulation during human pseudoelectro-mechanical dissociation (abstr). *Ann Emerg Med* 1990;19:491.

[f]Maha RJ, Yealy DM, Menegazzi JJ, et al. High-dose epinephrine in prehospital cardiac arrest: a preliminary report of 50 cases (abstr). *Ann Emerg Med* 1990;19:956.

[g]Barton CW, Callaham M. High-dose epinephrine significantly improves resuscitation rates in human victims of cardiac arrest (abstr). *Ann Emerg Med* 1990;19:490.

[h]Crespo SG, Spivey WH, Kelly JJ, et al. The effect of high-dose epinephrine on post-resuscitation cardiac output, catecholamines, and electrolytes in swine (abstr). *Ann Emerg Med* 1990;19:956.

[i]Callaham M, Barton C, Kayser S. Potential adverse effects of high-dose epinephrine in human survivors of cardiac arrest (abstr). *Ann Emerg Med* 1990;19:479.

[j]Brown CG, Department of Emergency Medicine, The Ohio State University, Columbus, Ohio: Personal communication, 1991.

citation efforts continued.[26] Administration of lidocaine to human patients with ventricular fibrillation increased the number of them converting to an effective rhythm, but did not alter resuscitation or survival rates significantly.[27] Unfortunately, several other studies have revealed that administration of lidocaine increased the electric energy required for defibrillation (often by as much as 100%), and that as blood concentrations of lidocaine decreased, the percentage of successful defibrillations increased.[28-30] Lidocaine may have a role after CPR in the prevention of recurrent malignant dysrhythmias, but is of questionable efficacy in the treatment of ventricular fibrillation.

Bretylium tosylate is a class-3 antiarrhythmic drug that also inhibits release of norepinephrine from adrenergic nerve endings.[25,27] Bretylium increases the action potential duration and prolongs the effective refractory period of ventricular myocardium without directly decreasing conduction velocity or automaticity.[25,27,31] In myocardial infarction, bretylium decreases the disparity in conduction velocity and action potential duration between normal and ischemic areas; this action may be important for bretylium's purported antifibrillating effects.[31] Studies on the effect of bretylium administration during ventricular fibrillation have yielded mixed results. Some investigators have indicated that bretylium (5 to 10 mg/kg) increased the threshold for ventricular fibrillation, but had a delay in onset of action (>10 minutes).[26,32] In a study comparing effectiveness of lidocaine and bretylium, clear superiority of either agent, relative to ease of resuscitation or to subsequent cardiac function, was not found in dogs with cardiac arrest.[33] However, bretylium appeared to be more effective than lidocaine in preventing recurrence of malignant ventricular dysrhythmias.[33] With lidocaine's rapid onset of action and bretylium's delayed effect, the combination of lidocaine and bretylium could be useful in the prevention of ventricular fibrillation after CPR.[26,32] Bretylium has inconsistent effects on the amount of current required for defibrillation when used prior to electric defibrillation; however, unlike lidocaine, it does not appear to measurably increase defibrillation threshold.[28,34,35] Although its actions are inconsistent, bretylium remains an important drug for consideration in the pharmacologic treatment of refractory ventricular fibrillation.

Breznock et al[36] have described the use of an acetylcholine/potassium mixture as an antifibrillating drug in dogs. Of 16 dogs in ventricular fibrillation, 12 (75%) were defibrillated to sinus rhythm with intracardiac administration of the acetylcholine/potassium mixture. The combination of the 2 drugs appears to be important in successful defibrillation, because administration of potassium or acetylcholine alone resulted in resuscitation rates of only 20 and 0%, respectively. Addition of acetylcholine is thought to increase potassium flux across the cell membrane, causing a marked increase in the velocity of repolarization and the arrest of all fibrillating myofibrils.[36] If fibrillation continued despite administration of the acetylcholine/potassium mixture, greater energy was required to electrically defibrillate the ventricles. Clinical information with regard to the use of acetylcholine/potassium mixtures in the treatment of ventricular fibrillation is lacking, because the mixture is commercially unavailable and has a limited shelf life.

Cardiac asystole has been found to be the initial dysrhythmia in 16 to 27% of human patients with cardiac arrest prior to hospital admission, and it has poor prognosis.[37] The ability of epinephrine to increase cardiac automaticity through activation of pacemaker β_1-adrenergic receptors would appear to be of value in treating asystole, although this mechanism has not been documented in clinical studies. Atropine often is administered to counter excessive parasympathetic neural tone that might be suppressing intrinsic sinoatrial automaticity during asystole and cardiac arrest. In a retrospective study of 107 human patients in cardiac arrest with initial asystole, 84 remained in refractory asystole after receiving epinephrine and sodium bicarbonate.[38] Of the 43 patients in this group also receiving atropine, 14% (6 of 43) were resuscitated successfully vs 0% in the control group. However, no patient who received atropine for refractory asystole lived to be discharged. Another study compared the efficacy of epinephrine, atropine, calcium chloride, and electric shock in the treatment of asystole during cardiac arrest.[37] Epinephrine, calcium chloride, and atropine infrequently altered the rhythm from asystole, whereas electric shock infrequently changed the rhythm from asystole when it appeared as the initial rhythm. However, electric shock was significantly more effective than epinephrine, atropine, or calcium chloride in altering the rhythm from asystole that appeared later in resuscitation. Ventricular fibrillation was the most common dysrhythmia after electric shock for asystole. Although asystole has a poor prognosis anytime during cardiac arrest regardless of treatment, administration of epinephrine and atropine commonly are advocated as treatments of choice for this dysrhythmia.

The present American Heart Association guidelines for treatment of EMD include administration of epinephrine, sodium bicarbonate, calcium chloride, and isoproterenol.[19] Whether these drugs aid in resuscitation from EMD remains controversial. In dogs with asphyxia-induced EMD, all 10 dogs receiving methoxamine were resuscitated quickly, vs slower responses in 5 of 10 dogs receiving atropine and in 6 of 10 receiving epinephrine.[39] Sanders[40] advocated advantages in the use of methoxamine in EMD for increasing aortic diastolic pressure, for maintaining the ratio of endocardial to epicardial blood flow, and possibly, for protecting against

dysrhythmias. In a prospective study involving 80 human patients with EMD, substantial difference in the abilities of methoxamine and epinephrine to resuscitate these patients was not demonstrated.[21] In 48 human patients with EMD refractory to epinephrine and bicarbonate treatment, administration of calcium chloride resulted in resuscitation of 16.7% (8 of 48) of the patients; however, only 1 patient who was resuscitated lived to be discharged from the hospital.[41] Evaluation of these patients' ECG revealed that those with electrocardiographic evidence of ischemia or with wide QRS complexes were most likely to respond positively to calcium chloride administration. The β_1-/β_2-adrenergic agonist isoproterenol may increase the force of weak cardiac contractions during EMD. Unfortunately, isoproterenol also may increase myocardial oxygen consumption and decrease coronary perfusion pressure at a time when oxygen delivery to the heart is limited.[19,41]

Naloxone, an opiate antagonist, has been shown to increase arterial pressure in hemorrhagic and septic shock.[42] Results from several studies have suggested that endogenous endorphins, released in response to physiologic stresses, may have myocardial depressant properties important in the pathogenesis of shock and cardiac arrest.[43] In dogs in cardiac arrest receiving conventional closed-thorax CPR, administration of naloxone did not significantly affect blood pressures or aortic flow.[43] However, naloxone administered after the development of EMD subsequent to electric shock resulted in all 4 dogs being successfully resuscitated.[43] This effect was thought to be mediated by catecholamine release and improved responsiveness of the heart to catecholamines after naloxone administration. Clinical experience will be necessary to substantiate beneficial effects of naloxone in animals with EMD.

Other Drugs

Other controversial drugs in the management of human and animal patients in cardiac arrest include sodium bicarbonate, glucose, calcium chloride, and calcium-channel blockers. The use of sodium bicarbonate in CPR has been debated vigorously. Proponents of bicarbonate administration describe the metabolic acidosis and its deleterious effects commonly seen during cardiac arrest.[1] Recently, however, the acid/base status of human patients in cardiac arrest has been documented more accurately.[44] Venous acidemia, caused by tissue production of CO_2 and impaired delivery of blood to the alveolar-capillary membrane, and arterial alkalemia, caused by the high ratio of pulmonary ventilation to perfusion associated with low blood flow during CPR, exist simultaneously. Improving blood flow during CPR and adequately ventilating the animal should result in more normal acid/base status.

Numerous adverse effects of bicarbonate administration have been documented, including hypernatremia and hyperosmolality; hypokalemia, resulting in increased incidence of dysrhythmias; decreased plasma concentration of ionized calcium; a shift in the oxyhemoglobin dissociation curve (with decreased oxygen delivery to the tissues); and a paradoxical CNS acidosis.[1,19,45] Many of these deleterious effects are related to production of CO_2, which diffuses more readily across cell membranes than bicarbonate does and aggravates intracellular acidosis.[45]

Current recommendations for correction of acid/base abnormalities during CPR are conservative with regard to bicarbonate administration. In human and animal patients that are not acidotic before cardiac arrest, acidosis may be controlled by use of adequate ventilation and cardiac compression.[19,45] The decision to administer bicarbonate ideally should be based on measurement of blood pH and CO_2 tension, and repeated infusion of bicarbonate in the absence of acidosis is contraindicated.[45] In animals with preexisting conditions in which acidosis is common, bicarbonate should be administered carefully at a dose (in mEq) equal to the base deficit (in mEq/L) multiplied by body weight (in kg) and then multiplied by 0.25 (volume of distribution in the extracellular space in L/kg).[45] Administration of additional sodium bicarbonate may be harmful when effective spontaneous circulation has been restored.

Conditions that promote metabolism of glucose to lactate in ischemic brain tissue have been known to increase cellular damage.[1,46] Preischemic hyperglycemia or administration of glucose during resuscitation increases tissue and plasma glucose concentrations, providing substrate for anaerobic glycolysis. During the ischemic episode, lactic acid accumulates to toxic amounts, resulting in cellular damage and permanent neurologic abnormalities. Studies done in adult cats that were administered 5% dextrose solutions during resuscitation revealed that neurologic recovery was markedly impaired in glucose-treated cats, and that the risk of postischemic brain damage increased with increasing blood glucose values.[47,48] In a retrospective study of human patients with cardiac arrest, poorer neurologic outcome was reported in those with high blood glucose concentration at hospital admission.[1] In a study of experimentally induced cardiac arrest in dogs, significant difference in neurologic score between dogs treated and not treated with glucose was not demonstrated.[k] However, in all dogs surviving >2 hours, the initial glucose value was significantly lower than that in dogs that died, indicating that prearrest blood glucose concentrations may be a predictor of mortality in cardiac arrest. These studies provide the rationale for avoiding administration of glucose during CPR unless the animal is hypoglycemic.

The routine use of calcium in cases of cardiac

[k]Gaver JW, Browning RG, Olson DW, et al. The effect of dextrose on outcome of cardiac arrest in a canine model (abstr). *Ann Emerg Med* 1990;19:609.

arrest has recently fallen into disfavor. Calcium entry into cells has been implicated as the trigger for a multitude of cellular reactions that may lead to cell death, including vasospasm, mitochondrial uncoupling, membrane degeneration, and production of cytotoxic compounds.[1,49-53] Activation of phospholipase A_2 results in arachidonic acid accumulation, with the subsequent production of free fatty acids. These acids act as detergents and disrupt cell phospholipid membrane integrity. Production of endoperoxides and leukotrienes contributes to formation of oxygen-derived free radicals, which further the severity of cellular damage. Postischemic myocardial contractile dysfunction (stunned myocardium) and neuronal death have been attributed to intracellular accumulation of calcium during the ischemic episode.[49] The use of calcium during CPR can be recommended only in cases of known hypocalcemia or in cases of cardiac arrest complicated by hyperkalemia, hypermagnesemia, and drug overdose with calcium-channel blockers.[1,49] Animal or human patients must be monitored closely by ECG during calcium administration.

Because of the deleterious effects of intracellular calcium accumulation during ischemia, much effort has been directed toward investigation of calcium-channel blocking agents in prevention of these postischemic problems. Administration of calcium-antagonist drugs at the onset of severe myocardial ischemia has been shown to be followed by increase in blood flow to ischemic areas, with decrease in the area of myocardial damage.[54] Calcium-channel blockers protect the performance and the cellular and subcellular structure of the myocardium subjected to ischemia during hypothermic cardiopulmonary bypass.[1,54] The increase in diastolic resting tension that normally follows reperfusion can be avoided with administration of calcium-blocking drugs.[49] Calcium-channel blockers also have been shown to increase the threshold of ischemic myocardium to ventricular fibrillation.[1,49,54] This antifibrillating action is thought to be caused, at least in part, by antagonism of enhanced adrenergic input to the heart that follows myocardial ischemia.[54] Several of the newer calcium-channel blockers, such as lidoflazine and nimodipine, have been shown to improve neurologic recovery after cardiac arrest in dogs and baboons when administered immediately after the return of spontaneous circulation.[50,51,53]

Summary

The goal of advanced life support in CPR must be to restore and maintain respiratory and hemodynamic effectiveness, and to correct the underlying dysrhythmia. Optimal basic life-support techniques must be continued to meet these goals. Many drugs have been suggested in the treatment of cardiac arrest, but unfortunately, drug effects are inconsistent and resuscitation rates remain low. Epinephrine, atropine, lidocaine, bretylium, and naloxone remain important drugs for consideration in CPR in most animals with cardiac arrest. The best chance of survival remains in early recognition of animals susceptible to arrest and in treatment of the underlying cause.

References

1. Schleien CL, Berkowitz ID, Traystman R, et al. Controversial issues in cardiopulmonary resuscitation. *Anesthesiology* 1989;71:133–149.
2. Ditchey RV, Lindenfeld J. Potential adverse effects of volume loading on perfusion of vital organs during closed-chest resuscitation. *Circulation* 1984;69:181–189.
3. Safar P. Resuscitation from clinical death: pathophysiologic limits and therapeutic potentials. *Crit Care Med* 1988; 16:923–941.
4. Harris LC, Kirimli B, Safar P. Augmentation of artificial circulation during cardiopulmonary resuscitation. *Anesthesiology* 1967;28:730.
5. Sanders AB, Atlas M, Ewy GA, et al. Expired PCO_2 as an index of coronary perfusion pressure. *Am J Emerg Med* 1985;3:147–149.
6. Yakaitis RW, Otto CW, Blitt CD. Relative importance of alpha- and beta-adrenergic receptors during resuscitation. *Crit Care Med* 1979;7:293-296.
7. Michael JR, Guerci AD, Koehler RC, et al. Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. *Circulation* 1984;69:822–835.
8. Stephens KA. Catecholamines and their use in shock. *Compend Contin Educ Pract Vet* 1983;5:671–680.
9. Livesay JJ, Follette DM, Fey KH, et al. Optimizing myocardial supply/demand balance with alpha-adrenergic drugs during cardiopulmonary resuscitation. *J Thorac Cardiovasc Surg* 1978;76:244–251.
10. Brown CG, Werman HA, Davis EA. The effect of high-dose phenylephrine versus epinephrine on regional cerebral blood flow during CPR. *Ann Emerg Med* 1987;16:743–748.
11. Brown CG, Davis EA, Werman HA, et al. Methoxamine versus epinephrine on regional cerebral blood flow during cardiopulmonary resuscitation. *Crit Care Med* 1987; 15:682–686.
12. Lindner KH, Ahnefeld FW, Pfenninger EG, et al. Effects of epinephrine and norepinephrine on cerebral oxygen delivery and consumption during open-chest CPR. *Ann Emerg Med* 1990;19:249–254.
13. Brown CG, Taylor RB, Werman HA, et al. Myocardial oxygen delivery/consumption during cardiopulmonary resuscitation: a comparison of epinephrine and phenylephrine. *Ann Emerg Med* 1988;17:302–308.
14. Olson DW, Thakur R, Stueven HA, et al. Randomized study of epinephrine versus methoxamine in prehospital ventricular fibrillation. *Ann Emerg Med* 1989;18:250–253.
15. Brillman JA, Sanders AB, Otto CW, et al. Outcome of resuscitation from fibrillatory arrest using epinephrine and phenylephrine in dogs. *Crit Care Med* 1985;13:912–913.
16. Brillman JA, Sanders A, Otto CW, et al. Comparison of epinephrine and phenylephrine for resuscitation and neurologic outcome of cardiac arrest in dogs. *Ann Emerg Med* 1987;16:11–17.
17. Bleske BE, Chow MSS, Zhao H, et al. Epinephrine versus methoxamine in survival post-ventricular fibrillation and cardiopulmonary resuscitation in dogs. *Crit Care Med* 1989; 17:1310–1313.
18. Brown CG, Birinyi F, Werman HA, et al. The comparative effects of epinephrine versus phenylephrine on regional cerebral blood flow during cardiopulmonary resuscitation. *Resuscitation* 1986;14:171–183.
19. American Heart Association. Standards and guidelines for cardiopulmonary resuscitation and emergency cardiac care. *JAMA* 1986;255:2905–2984.

20. Brunette DD, Jameson SJ. Comparison of standard versus high-dose epinephrine in the resuscitation of cardiac arrest in dogs. *Ann Emerg Med* 1990;19:8–11.

21. Turner LM, Parsons M, Luetkemeyer RC, et al. A comparison of epinephrine and methoxamine for resuscitation from electro-mechanical dissociation in human beings. *Ann Emerg Med* 1988;17:443–449.

22. Goetting MG, Paradis NA. High-dose epinephrine in refractory pediatric cardiac arrest. *Crit Care Med* 1989;17: 1258–1262.

23. Martin D, Werman HA, Brown CG. Four case studies: high-dose epinephrine in cardiac arrest. *Ann Emerg Med* 1990;19:322–326.

24. Safar P. Cardiopulmonary-cerebral resuscitation. In: Shoemaker WC, Ayres S, Grenvik A, eds. *Textbook of critical care.* 2nd ed. Philadelphia: WB Saunders Co, 1989;5–40.

25. Novotny MJ, Adams HR. New perspectives in cardiology: recent advances in antiarrhythmic drug therapy. *J Am Vet Med Assoc* 1986;189:533–539.

26. Chow MSS, Kluger J, DiPersio DM, et al. Antifibrillatory effects of lidocaine and bretylium immediately post-cardiopulmonary resuscitation. *Am Heart J* 1985;110:938–943.

27. Olson DW, Thompson BM, Darin JC, et al. A randomized comparison study of bretylium tosylate and lidocaine in resuscitation of patients from out-of-hospital ventricular fibrillation in a paramedic system. *Ann Emerg Med* 1984;13:807–810.

28. Chow MSS, Kluger J, Lawrence R, et al. The effect of lidocaine and bretylium on the defibrillation threshold during cardiac arrest and cardiopulmonary resuscitation. *Proc Soc Exp Biol Med* 1986;182:63–67.

29. Dorian P, Fain ES, Davy JM, et al. Lidocaine causes a reversible, concentration-dependent increase in defibrillation energy requirements. *J Am Coll Cardiol* 1986;8:327–332.

30. Echt DS, Black JN, Barbey JT. Evaluation of antiarrhythmic drugs on defibrillation energy requirements in dogs. *Circulation* 1989;79:1106–1117.

31. Koch-Weser J. Bretylium. *New Engl J Med* 1979; 300:473–477.

32. Hanyok JJ, Chow MSS, Kluger J, et al. Antifibrillatory effects of high-dose bretylium and a lidocaine-bretylium combination during cardiopulmonary resuscitation. *Crit Care Med* 1988;16:691–694.

33. Vachiery JL, Reuse C, Blecic S, et al. Bretylium tosylate versus lidocaine in experimental cardiac arrest. *Am J Emerg Med* 1990;8:492–495.

34. Dorian P, Fain ES, Davy JM, et al. Effect of quinidine and bretylium on defibrillation energy requirements. *Am Heart J* 1986;112:19–25.

35. Koo CC, Allen JD, Pantridge JF. Lack of effect of bretylium tosylate on electrical ventricular defibrillation in a controlled study. *Cardiovasc Res* 1984;18:762–767.

36. Breznock EM, Kagan KG, Attix ES. Chemical cardioversion of electrically induced ventricular fibrillation in dogs. *Am J Vet Res* 1978;39:971–975.

37. Ornato JP, Gonzales ER, Morkunas AR, et al. Treatment of presumed asystole during prehospital cardiac arrest: superiority of electrical countershock. *Am J Emerg Med* 1985; 3:395–399.

38. Stueven HA, Tonsfeldt DJ, Thompson BM, et al. Atropine in asystole: human studies. *Ann Emerg Med* 1984;13: 815–817.

39. Redding JS, Haynes RR, Thomas JD. Drug therapy in resuscitation from electromechanical dissociation. *Crit Care Med* 1983;11:681–684.

40. Sanders AB. The roles of methoxamine and norepinephrine in electro-mechanical dissociation. *Ann Emerg Med* 1984;13:835–839.

41. Stueven HA, Thompson B, Aprahamian C, et al. The effectiveness of calcium chloride in refractory electro-mechanical dissociation. *Ann Emerg Med* 1985;14:626–629.

42. Reynolds DG, Gurill NG, Vargish T, et al. Blockade of opiate receptors with naloxone improves survival and cardiac performance in canine endotoxic shock. *Circ Shock* 1980;7:39–48.

43. Rothstein RJ, Niemann JT, Rennie CJ, et al. Use of naloxone during cardiac arrest and CPR: potential adjunct for post-countershock electro-mechanical dissociation. *Ann Emerg Med* 1985;14:198–203.

44. Weil MH, Rackow EC, Trevino R, et al. Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. *New Engl J Med* 1986;315:153–156.

45. Van Pelt DR, Wheeler SL, Wingfield WE. The use of bicarbonate in cardiopulmonary resuscitation. *Compend Contin Educ Pract Vet* 1990;12:1393–1399.

46. Browning RG, Olson DW, Stueven HA, et al. 50% dextrose: antidote or toxin? *Ann Emerg Med* 1990;19:683–687.

47. Nakakimura K, Fleischer JE, Drummond JC, et al. Glucose administration before cardiac arrest worsens neurologic outcome in cats. *Anesthesiology* 1990;72:1005–1011.

48. Hossman KA. Resuscitation potentials after prolonged global cerebral ischemia in cats. *Crit Care Med* 1988; 16:964–971.

49. Hughes WG, Ruedy JR. Should calcium be used in cardiac arrest? *Am J Med* 1986;81:285–296.

50. White BC, Winegar CD, Wilson RF, et al. Possible role of calcium blockers in cerebral resuscitation: a review of the literature and synthesis for future studies. *Crit Care Med* 1983; 11:202–207.

51. Winegar CP, Henderson O, White BC, et al. Early amelioration of neurologic deficit by lidoflazine after fifteen minutes of cardiopulmonary arrest in dogs. *Ann Emerg Med* 1983;12:471–477.

52. Shapiro HM. Post-cardiac arrest therapy: calcium entry blockade and brain resuscitation. *Anesthesiology* 1985;62: 384–387.

53. Steen PA, Gisvold SE, Milde JH, et al. Nimodipine improves outcome when given after complete cerebral ischemia in primates. *Anesthesiology* 1985;62:406–414.

54. Resnekov L. Calcium antagonist drugs—myocardial preservation and reduced vulnerability to ventricular fibrillation during CPR. *Crit Care Med* 1981;9:360–361.