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risk of developing postbypass renal failure seems to be a function of the patient's underlying renal function (also affected by age) and the perioperative circulatory status. The histologic changes that accompany renal impairment after cardiopulmonary bypass are characteristic of tubular necrosis. The tubular cells seem to be the most susceptible to acute reductions in renal perfusion.³¹

Management

There are three agents (so-called renoprotective drugs) that might be used during CPB to prevent an ischemic insult to the kidneys. Mannitol used in the CPB priming fluid may moderate ischemic insult, probably by volume expansion and hemodilution. It also initiates an osmotic diuresis, which prevents tubular obstruction and may serve as a free radical scavenger. Furosemide appears to improve renal blood flow when given during bypass. So-called renal dose dopamine (1 to 2.5 $\mu\text{g}/\text{kg}/\text{min}$ based on ideal body weight) may maintain renal blood flow and urine output. Once renal failure has developed, none of these drugs is likely to offer any beneficial effect. A megadose of furosemide (200 to 300 mg) may be tried, but if there is no diuretic response, it should not be repeated. Similarly, a single dose of mannitol (12.5 to 25 mg) either with or without furosemide could be tried but not repeated if there is no effect. Whenever possible, it is advisable to avoid potentially nephrotoxic agents in the early postoperative period. Examples of such include radiologic contrast agents, aminoglycoside antibiotics, and angiotensin-converting enzyme inhibitors.

POSTOPERATIVE GASTROINTESTINAL DYSFUNCTION

Gastrointestinal Consequences of Cardiopulmonary Bypass

The gastrointestinal consequences of CPB appear to be minimal. Reviews of the subject report a 1 percent prevalence.^{32,33} Most patients are eating within 24 to 48 h after an uncomplicated elective procedure. The limited investigations of the gastrointestinal tract after cardiac surgery have found a slight decrease in hepatic and pancreatic blood flow during cooling and rewarming on bypass and a decrease in gastric pH.^{30,34} Transient elevations in liver function tests and hyperamylasemia may occur after cardiac surgery, and the risk factors include long CPB time, multiple transfusions, and multiple valve replacements. Appearance of jaundice portends a poor prognosis.³⁵ Severe gastrointestinal complications are usually ischemic in nature and are often associated with a low-output syndrome.³⁰ The use of opioids as part of general anesthesia and postoperative pain management contributes to gastrointestinal dysfunction (cramping, ileus, constipation) and to postoperative nausea and vomiting. The nausea and vomiting can be minimized by use of a naso- or orogastric tube to maintain gastric decompression intraoperatively and early in the post-

operative period, with the additional benefit of improving thoracoabdominal compliance to positive-pressure ventilation.

POSTOPERATIVE METABOLIC DISORDERS

Potassium Imbalance

There are multiple factors that can produce large and rapid shifts in the serum potassium levels during and after CPB. These factors include the following: (1) The patient receives a high-potassium cardioplegia solution during surgery; (2) some degree of renal dysfunction is likely to be present, with associated oliguria and decreased clearance of potassium; (3) low cardiac output states are accompanied by oliguria and acidosis; (4) hemolyzed red cells release potassium; (5) potassium is lost by diuresis; and (6) diabetes mellitus interferes with cellular uptake of potassium unless insulin is infused intra- and postoperatively. The principal detrimental effects of these potassium shifts is on the electrical activity of the heart. The electrocardiographic signs of hyperkalemia and hypokalemia are described in Chap. 12. The electrocardiographic changes of hyperkalemia do not necessarily appear in the classic progressive manner; they are more related to the rate of rise in serum potassium rather than to the absolute serum concentration. The therapy of severe hyperkalemia should include counteracting the toxic cardiac effects of the elevated potassium with intravenous calcium gluconate or calcium chloride and lowering the serum level of potassium with sodium bicarbonate and/or administration of regular insulin and glucose. Hypokalemia does not usually become clinically evident until the serum potassium concentration is less than 2.5 meq/L, and at these levels it can be associated with severe ventricular tachyarrhythmias. Another consequence of potassium depletion is metabolic alkalosis as the hydrogen ions replace potassium ions within the cells. Hypokalemia is treated with the intravenous administration of KCl at a rate of no more than 10 to 15 meq/h. The serum potassium rises approximately 0.1 meq/L for each 2 meq of KCl administered. Large doses of KCl should be administered by a central venous catheter because of the caustic effect of potassium on peripheral veins.

Hypomagnesemia

Hypomagnesemia is common following cardiac surgery using CPB. Magnesium mimics potassium in its effects on the electrical activity of the heart. The cause of the hypomagnesemia is unknown, but it is probably multifactorial. Many patients will be hypomagnesemic preoperatively due to the use of loop diuretics, thiazides, digoxin, or alcohol and to the effects of type I diabetes mellitus. Magnesium is usually lost in the urine during CPB. Patients with postoperative hypomagnesemia develop atrial and ventricular dysrhythmias more frequently and require more prolonged mechanical ventilatory

THERAPEUTIC CONTROVERSIES

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CONTROVERSIES IN CARDIOPULMONARY RESUSCITATION:

PEDIATRIC CONSIDERATIONS

Rosalie Sagraves and Claudia Kamper

ABSTRACT: This article addresses some therapeutic controversies concerning medications that may be needed during advanced pediatric life support (APLS) and the routes of administration that may be selected. The controversies that are discussed include the appropriateness and selection of various routes for drug administration during APLS; the determination of whether epinephrine hydrochloride is the adrenergic agent of choice for APLS and its appropriate dose; treatment of acidosis associated with a cardiopulmonary arrest; recommendations for atropine sulfate doses; and the role, if any, of calcium in APLS. Background information differentiating pediatric from adult cardiopulmonary arrest is presented to enable the reader to have a better understanding of the specific needs of children during this life-threatening emergency. The article also presents an overview of various drugs used for APLS and a table of their typically recommended doses and routes of administration.

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CHILDREN WHO EXPERIENCE CARDIAC ARREST typically have a poor prognosis.^{1,4} Pediatric survival rates from cardiac arrests that occur in the prehospital setting average 7 percent (3 percent if arrests were unwitnessed and 15 percent if witnessed by paramedics).² Such figures are low when compared with an overall survival rate of 20 percent for adults who experienced cardiac arrests in a similar setting.⁴ From

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This article is approved for continuing education credit.

time of cardiac arrest to eventual hospital discharge, survival rates for pediatric patients typically have ranged from 5.5 to 21.0 percent when the arrest occurred in a hospital.¹ Recently, more optimistic survival rates have been reported for pediatric patients who experience cardiac arrest. In a prospective study evaluating the use of high-dose IV epinephrine hydrochloride (0.2 mg/kg) for pediatric cardiac arrest, Goetting and Paradis reported that 40 percent of the pediatric patients (8/20) survived to be discharged from the hospital. Goetting and Paradis stated that all cardiac arrests had been witnessed and all 20 patients received cardiopulmonary resuscitation (CPR) and appropriate medications within seven minutes after the arrest began.⁵ These same investigators previously published a series of case reports in which four of seven patients survived to be discharged from the hospital after receiving at least one dose of epinephrine 0.2 mg/kg IV during prolonged CPR.⁶ Survival rates from pediatric cardiac arrest must be differentiated from those for respiratory arrest, because overall survival rates from the latter may be higher (17–55 percent).¹

Reasons for poor pediatric survival rates after cardiac arrest include the inability of bystanders in the prehospital setting to respond to what is happening to the child, the lack of trained paramedics who can recognize and handle the pediatric cardiac arrest patient, and a diversity in the etiologies for cardiac arrest in children. Other reasons include the evolution of cardiac arrest from respiratory arrest in many children, a high incidence of asystole, and possibly the receiving of inadequate epinephrine doses.^{1,2,5,6}

Etiologies for cardiac arrest in infants and children commonly include near-drowning, infection, sudden infant death syndrome, poisoning, trauma, asphyxia, and aspiration of a foreign body.

Asystole and bradyarrhythmias account for approximately 80–90 percent of all arrhythmias reported in children who experience cardiac arrest, whereas all ventricular

arrhythmias account for an additional 10 percent.²³ This percentage differs from cardiac arrests that occur in adults, in whom ventricular fibrillation is more common.³ Children are more likely to experience a bradyarrhythmia or asystole because many pediatric patients have respiratory arrest prior to cardiac involvement. Respiratory arrest can cause significant hypoxia and acidosis, which may lead to a bradyarrhythmia, asystole, or cardiac arrest.

In this article we review many aspects of pharmaceutical intervention in pediatric CPR or advanced pediatric life support (APLS). We emphasize areas of therapeutic controversy, including methods for drug administration, the selection of the best adrenergic agent for initial administration during CPR, and the appropriate dose for the adrenergic drug and its route of administration. We also discuss the treatment of acidosis; recommendations for pediatric atropine sulfate doses; the role, if any, of calcium in cardiac arrest; and the place of other pharmaceutical agents that may be used during APLS. The information presented here is based on adult patient and animal data as well as pediatric literature, because little specific information about drugs used for APLS is available.

Methods for Drug Administration

Peripheral and central IV routes traditionally have been used to deliver drugs needed for resuscitation. Difficulty obtaining venous access during CPR, particularly in infants and children, is a significant problem facing health-care professionals. Endotracheal (ET) and intraosseous (IOS) routes have therefore been suggested as viable alternatives to peripheral or central venous access. Changes in administration techniques for drug delivery during cardiopulmonary resuscitation are continually being investigated to achieve better patient outcomes, but controversy often surrounds technique modifications until they are adequately shown to be beneficial. Additionally, effective doses of drugs used routinely during resuscitation remain controversial as alternative routes for drug administration are endorsed.

ENDOTRACHEAL DRUG ADMINISTRATION

Several drugs used for APLS can be administered via the ET route (Table 1). Theoretically, in addition to the availability of rapid access, this route may be advantageous because of the rapid absorption and distribution of drugs to the arterial tree.¹³ An extensive pulmonary surface area with perfusion makes this route suitable for the administration of drugs exhibiting physical and chemical properties that allow them to be absorbed across the alveolar-capillary membrane. Comparisons of this route to IV administration have been made by several investigators who have shown similar times to reach peak drug concentrations, but who also have shown significantly decreased concentrations (10–33 percent) and associated poor clinical responses.^{14–16} A depot effect also may occur, which may result in a delayed, exaggerated pharmacologic response, such as hypertension with epinephrine.^{14,17} Thus, the optimal dose to provide equivalent clinical response remains to be determined for all drugs used endotracheally. Delivery techniques for optimal drug absorption, presumably via the small airways, have not been thoroughly studied. Drug dilution with saline has been suggested to enhance delivery to small airways, as well as minimize detrimental effects on arterial blood gases.¹⁸ Alternatively, the dose of drug may be given followed by a saline bolus. Chernow et al. found that intratracheal administration of epinephrine 1:10 000 as a 5-mL aliquot instilled down the ET tube produced significantly increased plasma epinephrine concentrations above baseline within one minute of administration.¹⁹

Diluent selection also may be important when using the ET route for drug administration. Redding et al. compared equivalent doses of undiluted epinephrine ET with epinephrine ET diluted to 10 mL with either water or saline in a canine arrest model. They found water to be the superior diluent, presumably because of better absorption by the lung.²⁰ Water, however, may cause depression of pH and pO₂ and elevation of pCO₂. The reader is directed to a review of ET administration of drugs commonly used in CPR for further information.²¹

Table 1. Drug Dosing Guidelines for Pediatric Cardiopulmonary Resuscitation¹⁷

| DRUG | BOLUS DOSE | ROUTE | CONTINUOUS INFUSION DOSE | REMARKS |
|--------------------|------------|-------------|--|---|
| Atropine sulfate | 0.02 mg/kg | IV, ET, IOS | NR | minimum dose of 0.1 mg should be given to avoid paradoxical bradycardia |
| Bretylium tosylate | 5 mg/kg | IV | NR | patient should be monitored closely for hypotension |
| Calcium chloride | 20 mg/kg | IV | NR | administer slowly |
| Dobutamine HCl | NR | IV | initiate at 5–10 µg/kg/min; titrate to effect; maximum 20 µg/kg/min | |
| Dopamine HCl | NR | IV | initiate at 5–10 µg/kg/min; titrate to effect; maximum 20 µg/kg/min | administer through central line; extravasation may be treated with phentolamine; ⁴ use of the IOS route has been reported ⁹ |
| Epinephrine HCl | 0.01 mg/kg | IV, ET, IOS | initiate at 0.1 µg/kg/min; titrate to effect; maximum 1 µg/kg/min | |
| Lidocaine HCl | 1 mg/kg | IV, ET, IOS | initiate at 20 µg/kg/min; maximum 50 µg/kg/min | |
| Naloxone HCl | 0.1 mg/kg | IV | may be administered as a continuous infusion in place of repeat boluses; 0.04–0.16 mg/kg/h ¹⁰ | |
| Sodium bicarbonate | 1 mEq/kg | IV | also may be given by slow IV infusion | not recommended to be given by ET route because of volume necessary; infuse slowly; use of the IOS route has been reported ^{11,12} |

ET = endotracheal; HCl = hydrochloride; IOS = intraosseous; NR = not recommended.

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INTRAOSSEOUS DRUG ADMINISTRATION

The technique of IOS delivery was first used clinically in the 1940s.²² It subsequently met with mixed success as techniques for long-term venous access were developed, and only recently has it been recognized for its benefits in CPR. Despite advancements in IV access techniques, ease and speed of gaining IV access during CPR is difficult and time consuming. A review of time required for gaining IV access in pediatric arrests reveals a significant delay of greater than ten minutes in 24 percent of patients and failure to gain IV access in 6 percent of patients. Those with successful CPR outcomes tended to have earlier IV access.²³ Therefore, rapid achievement of IV access appears to be critical to the success of resuscitation efforts.

The IOS route has the advantage of being rapid,¹¹ easy to master,^{11,24-26} and applicable to both the prehospital and emergency department settings.²⁵⁻²⁸ It allows for fluids, medications, and blood products to be administered.^{25,27,29-31} Epinephrine,^{9,11} sodium bicarbonate,^{11,22} atropine,^{11,29} dopamine hydrochloride,⁹ diazepam,³² isoproterenol hydrochloride,¹¹ pancuronium bromide,¹¹ phenytoin sodium,^{11,33} phenobarbital sodium,¹¹ succinylcholine chloride,²⁹ dexamethasone sodium phosphate, lidocaine hydrochloride, heparin sodium, diazoxide,²⁸ and antibiotics³² are some drugs that have been delivered intraosseously. Table 1 contains a list of drugs that have been administered intraosseously during APLS. Intraosseous infusions are indicated in emergent situations when peripheral or central IV access is unsuccessful or would waste valuable time. Protocols have been developed that provide guidelines for the use of the IOS route. Some advise trying two quick attempts at peripheral IV access before attempting the IOS route,²⁵ and another suggests using the IOS route after five minutes of resuscitative efforts without successful placement of a peripheral cannula.³⁴

The characteristics of IOS delivery have been shown to be similar to IV drug delivery with minimal alterations early in delivery.²⁹ Following confirmation of needle placement (see References 25, 27, 29, and 30 for techniques for placing lines), fluid delivery may initially be sluggish because of obstruction of the needle by marrow contents.^{28,29} A saline flush may be used to clear the needle in preparation for a constant infusion. Achievable flow rates for the IOS route may be somewhat lower than those for the peripheral IV route; therefore, this route may not be optimal for volume resuscitation.²⁹ Rapid or slow administration of drugs intraosseously results in disposition similar to that for IV delivery.³⁵ Peak drug concentrations, although slightly delayed, within minutes are equivalent to IV injection and remain elevated somewhat longer because of a depot effect of the marrow cavity. A saline flush may further enhance drug delivery by displacing the drug from the cavity into the venous circulation surrounding the bone.³⁶

The complications associated with this route of administration over the years have been thoroughly reviewed by Rosetti et al.²⁷ The most frequent complication cited by these authors was osteomyelitis (0.6 percent; 27/4270 infusions), which apparently was related to preexisting bacteremia, hypertonic fluid administration, and prolonged duration of IOS catheter use.^{27,37} Other reported complications include improper placement of the needle resulting in extravasation of fluid or medication, failure to penetrate the marrow cavity, clotting of the needle, abscess, local cellulitis,

and pressure necrosis. Fat and bone marrow emboli to the lungs have been reported in autopsy specimens from two pediatric patients, but in a controlled trial in the canine model, the presence of pulmonary fat emboli did not appear to compromise the resuscitative effort or clinical outcome.³⁸ True contraindications to the IOS route exist and include fractures, bone disorders such as osteogenesis imperfecta, cellulitis, or burns at the site.³⁷ Preexisting bacteremia may also be a contraindication. The IOS route appears to be an important access route in the emergency pediatric setting and it may become more widely used in the future.

Medications Administered During Cardiopulmonary Resuscitation

EPINEPHRINE (ADRENALIN)

APLS guidelines recommend using epinephrine for a pediatric patient who has a sustained cardiac arrest; for stabilizing the arrested child after cardiac rhythm has been restored but whose blood pressure, perfusion, or cardiac rhythm remains unstable; or for a child who is hypotensive with inadequate cardiac output.^{3,39} Epinephrine use in these situations is not controversial, but controversy does surround dosage selection and the route of administration. The optimal choice of adrenergic agent also has been controversial.

Epinephrine is a catecholamine that possesses alpha- and beta-adrenergic properties. Its desired pharmacologic actions for treating cardiac arrest include establishment of an effective coronary artery perfusion pressure, with preferential coronary and cerebral blood flow; improved myocardial contractility; stimulation of spontaneous myocardial contractility; and increased myocardial susceptibility to electrical defibrillation.^{4,7,40}

The optimal epinephrine dose or dosage range needed to achieve these desired effects is currently under debate for both children and adults.^{5,6,40-44} Goetting and Paradis have raised the issue of whether IV doses of epinephrine 0.01 mg/kg for infants and children, as recommended in APLS guidelines, are suboptimal for pediatric CPR.^{5,6} Some researchers have questioned whether the doses of epinephrine 0.5-1 mg IV (approximately 7-15 µg/kg when calculated for a 70-kg patient) that are recommended by advanced cardiac life support (ACLS) guidelines are adequate for adults.⁴⁰⁻⁴⁴ The results from several animal resuscitation studies, as well as human adult case reports and preliminary studies, indicate that higher epinephrine doses than are currently recommended in ACLS guidelines may be required for cardiac resuscitation.^{40,44-52} Questions that need to be answered include whether all patients who experience cardiac arrest need higher epinephrine doses for resuscitation and, if such doses are instituted, whether they will be more beneficial than harmful when compared with standard doses.

Animal studies offer insight into the controversy over IV epinephrine dosage during CPR. Redding and Pearson observed that doses of epinephrine 1 mg were needed to resuscitate dogs following cardiac arrest, but it must be remembered that these 1-mg doses were administered to dogs that weighed 6.5-14 kg (approximately 70-150 µg/kg).⁵³⁻⁵⁵ Kirimili et al. found that epinephrine 50 µg/kg was needed to resuscitate study animals,⁴⁶ whereas Kosnick et al. observed that increasing epinephrine doses from 15 to 150

$\mu\text{g}/\text{kg}$ elevated aortic diastolic pressures and prolonged epinephrine's effectiveness in dogs being resuscitated.⁴⁹ Brown et al. have published animal studies evaluating the effects of epinephrine on regional myocardial and cerebral blood flow.⁵⁰⁻⁵² In two studies, epinephrine was administered in doses of 0.02, 0.2, or 2.0 mg/kg IV to swine that had experienced ventricular fibrillation. The 0.2- and 2.0-mg/kg doses increased myocardial and cerebral blood flow, whereas the dose of 0.02 mg/kg did not.^{50,51}

Goetting and Paradis compared 20 children enrolled in a prospective study who received high doses of epinephrine (0.2 mg/kg IV) during pediatric CPR to 20 historic controls (matched for age, vasopressor use, time to CPR, and time to the first dose of epinephrine) who received standard doses of epinephrine (0.01 mg/kg IV) under similar conditions. All of the children in the prospective group had failed at least two standard IV epinephrine doses prior to study enrollment. Fourteen children had a return of spontaneous circulation within five minutes after high-dose epinephrine, whereas none of the historic controls responded to standard epinephrine doses. Additionally, eight of the patients enrolled in the prospective study survived to hospital discharge.⁵ Goetting and Paradis also published an article describing four children, out of a total of seven, who ultimately were discharged from the hospital after receiving at least one dose of epinephrine 0.2 mg/kg IV during prolonged CPR.⁶

Because pediatric experience with high-dose IV epinephrine administration is limited, the following information gained from experiences in adults may be helpful. Epinephrine doses of 70–140 $\mu\text{g}/\text{kg}$ IV were used by Koscove and Paradis to resuscitate two patients unresponsive to standard epinephrine doses during prolonged CPR. Both patients had a return of spontaneous circulation, but only one survived to discharge.⁴⁵ Gonzalez et al. reported a dose-response pressor effect on both systolic and diastolic blood pressure in ten adults who received increasing doses of epinephrine 1, 3, and 5 mg IV at five-minute intervals. All of these patients had experienced prehospital cardiac arrest and were still in arrest upon hospital arrival. None of them had spontaneous circulation after receiving epinephrine 3 mg; one responded to the 5-mg dose but expired shortly thereafter.⁴⁰ Martin et al. reported that four patients who did not respond to standard IV epinephrine doses prior to hospital admission, and who arrived in the emergency department with nonperfusing rhythms of at least 20 minutes' duration, attained systolic blood pressures ranging from 134 to 220 mm Hg within five minutes after receiving doses of epinephrine 0.12–0.22 mg/kg IV. All four patients had severe brain damage secondary to prolonged CPR and brain ischemia; none survived to hospital discharge.⁴⁶ Paradis et al. reported that high-dose epinephrine (0.2 mg/kg) administered to 32 patients with cardiac arrest refractory to ACLS (including multiple doses of epinephrine 1 mg IV) resulted in increases of coronary perfusion pressures by 11.3 ± 10.0 mm Hg compared with increases of 3.7 ± 5.0 mm Hg after standard epinephrine doses. The investigators stated that the use of high doses of epinephrine would be more likely than standard doses to increase coronary perfusion pressure to at least 15 mm Hg, which is needed to adequately perfuse the coronary arteries.⁴⁴

Epinephrine administered in high doses may or may not be detrimental to patients being resuscitated; this is difficult

to determine. Catecholamine administration has been associated with vascular injury and a type of myocardial injury called contraction band necrosis. This latter injury was reported to occur more frequently in pediatric patients who received catecholamines during unsuccessful resuscitation efforts than in those who did not receive epinephrine, but this type of damage can also occur after myocardial ischemia and sudden cardiac death.^{5,54-58} Theoretically, high doses of epinephrine used during CPR could increase myocardial oxygen demand more than oxygen delivery. This would be especially detrimental to the myocardium if ischemia and an arrhythmia such as ventricular fibrillation, which increases oxygen demand, already existed.⁵⁶ Case reports of epinephrine overdoses in patients not needing CPR have noted adverse effects such as pulmonary edema, hypertension, cardiac ischemia, hypokalemia, and hyperglycemia.^{57,59,60}

Callahan et al. reported that there were no significant differences in the incidence of hypertension, pulmonary edema, arrhythmias, new ischemic changes in electrocardiogram, creatine kinase concentrations (total or myocardial band), or glucose, bicarbonate, potassium, and magnesium serum concentrations among adults receiving high-dose IV epinephrine (defined as a single IV dose ≥ 50 $\mu\text{g}/\text{kg}$ or a total dosage of ≥ 2.8 $\mu\text{g}/\text{kg}/\text{min}$) and those who received standard doses (doses lower than high-dose epinephrine). Only lower serum calcium concentrations were noted in the high-epinephrine group. The authors concluded that patients who received higher epinephrine doses during CPR did not experience a greater incidence of epinephrine-associated complications, because there may have been a "down-regulation of adrenergic receptors, altered sensitivity to catecholamines at different stages of cardiac arrest, and altered pharmacokinetics during cardiac arrest."⁵⁷ Although the results from this study present evidence that high-dose epinephrine may not increase patient risk, it should be noted that the study was a nonrandomized, retrospective one in which no epinephrine dosage stratification was done prior to analysis. In addition, only a limited number of patients qualified for analysis (33 in the high-dose group, 35 in the standard-dose group), and those who did not survive for at least six hours after resuscitation were not included.^{56,57}

The optimal epinephrine dose for pediatric patients who require CPR is currently unknown, and whether the dose should be the same for all patients requiring CPR is debated. Some patients respond quickly to low doses of epinephrine whereas others, especially those without adequate perfusion, may require high doses of epinephrine either initially or after they fail to respond to standard doses of epinephrine. Goetting and Paradis support the use of high doses of epinephrine (0.2 mg/kg IV) after a pediatric patient fails to respond to two standard doses.⁵ Brown and Kelen urge caution regarding this recommendation because patients in the study by Goetting and Paradis had various etiologies for their cardiac arrests (e.g., asphyxia, aspiration, sepsis, hypovolemia, trauma, sudden infant death syndrome) and none sustained arrest secondary to underlying cardiac disease. Brown and Kelen recommend that high-dose epinephrine should not be routinely used until more information is available.⁶¹

Studies are needed to determine whether the administration of higher epinephrine doses early in resuscitation can make a difference not only in a patient's cardiac outcome

but also in his neurologic status before high-dose epinephrine can be used on more than an experimental basis. A prospective, multicenter study currently is being conducted. The Ohio State University and the University of Pittsburgh to compare the efficacy of various doses of IV epinephrine for adult cardiac arrest in a prospective manner. When completed, such a study should provide additional information to answer the question of whether high-dose epinephrine has a place in cardiac resuscitation.⁶⁶

Epinephrine as a continuous infusion also has been recommended for cardiac arrest.¹ Animal studies using epinephrine infusions of 4 µg/kg/min (doses much higher than the 0.1–1.0 µg/kg/min rates for epinephrine infusion currently recommended for pediatric patients) after initial loading doses have shown favorable outcomes on myocardial and cerebral perfusion and blood flow.^{62,63} Callaham has stated that continuous infusions of IV epinephrine may be too slow or too unpredictable to adequately deliver desired concentrations of epinephrine to patients who have poor perfusion.⁶³ Further studies are needed to determine if continuous epinephrine infusions are effective in patients who have experienced cardiac arrest, and if so, what administration rate would be most appropriate.

Animal and human studies have been performed to help decide which adrenergic agent is most appropriate for use during CPR. Using animal studies, Redding and Pearson observed that phenylephrine and methoxamine (pure alpha-adrenergic agents) were as efficacious as epinephrine for cardiac arrest.^{53,54} Additionally, alpha- and beta-adrenergic blockade studies by Yakaitis et al.⁶⁴ and Otto et al.⁶⁵ suggest that it is the alpha-adrenergic properties of epinephrine, and not its beta effects, that are responsible for restoring circulation during CPR. If alpha effects are more important than beta effects for cardiac resuscitation then, during CPR, one would expect pure alpha-adrenergic drugs to be more effective than epinephrine, which has mixed alpha and beta activity.

Two studies in human adults have further addressed this issue. In a double-blind study, Turner et al. showed no difference in the survival of 80 adults who received ACLS-indicated doses of either epinephrine or methoxamine after cardiac arrest. (The authors considered epinephrine 1 mg equivalent to methoxamine 10 mg.) Patients were evaluated for survival for less than one hour, 1–6 hours, 6–12 hours, 12–24 hours, and longer than 24 hours.⁶⁶ In a randomized study, Olson et al. showed a higher resuscitation rate for patients who received epinephrine 0.5 mg IV after ventricular fibrillation (n=51) than for those who received methoxamine 5 mg IV (n=51); i.e., 49.0 and 27.5 percent, respectively (p<0.02). Those in the epinephrine group received 2.8 ± 1.3 doses during resuscitation whereas those in the methoxamine group received 3.1 ± 1.4 doses (p<0.02). Of those in the epinephrine group, 19.6 percent were discharged alive, whereas in the methoxamine group 7.8 percent survived to discharge (p<0.08).⁶⁷

The selection of the most appropriate adrenergic agent to be used during CPR has been addressed in animal studies in which epinephrine, when used for cardiac arrest, was compared with the alpha₁-selective adrenergic agents methoxamine and phenylephrine.^{68,72} Brown et al. compared IV epinephrine and methoxamine in two animal studies. Epinephrine 0.2 mg/kg administered to swine that had experienced ventricular fibrillation resulted in better defibrillation

outcomes and increased myocardial and cerebral blood flow when compared with methoxamine administered in doses of 0.1, 1, or 10 mg/kg. Epinephrine did not produce these same results when doses of 0.02 mg/kg were administered.^{68,69} Studies also were performed to compare epinephrine 0.2 mg/kg IV with phenylephrine 1 or 10 mg/kg administered to swine as previously explained.^{70,71} Regional cerebral blood flow was increased in animals receiving epinephrine when compared with those receiving phenylephrine 1 mg/kg; there was no difference in cerebral flow when animals receiving epinephrine were compared with those receiving phenylephrine 10 mg/kg (p<0.05).⁷⁰ In a second study, animals receiving epinephrine demonstrated better regional myocardial blood flow than did those receiving phenylephrine. Additionally, 80 percent of the swine given epinephrine were resuscitated whereas none in the phenylephrine group survived.⁷¹ Brillman et al. demonstrated no difference in neurologic or cardiovascular outcomes in dogs that received either epinephrine 1 mg or phenylephrine 10 mg IV after cardiac arrest.⁷²

Although epinephrine possesses alpha- and beta-adrenergic activity, it appears to be the adrenergic agent of choice.¹ Better survival rates after epinephrine administration have been demonstrated in several previously discussed studies.^{68,71} These rates may occur because epinephrine has both alpha₁ and alpha₂ effects (exhibited at high doses) whereas phenylephrine and methoxamine are pure alpha₁-agonists. Alpha₁-receptors are predominant in the walls of resistance blood vessels, whereas alpha₂-receptors are located near the lumen of these vessels. Furthermore, alpha₁-receptors "appear to be activated primarily by neuronally-released norepinephrine, whereas the alpha₂-receptors are activated by circulating catecholamines."⁷⁰ Therefore, if the effect of circulating catecholamines predominates over neuronally released catecholamines during cardiac arrest, then epinephrine may be more beneficial. This appears to be reasonable because Brown et al. have shown that epinephrine, more than phenylephrine and methoxamine, increases myocardial oxygen delivery over myocardial oxygen consumption; this results in increased blood flow to various regions of the heart and brain.^{68,70} The initial use of dopamine or dobutamine as a catecholamine of choice rather than epinephrine will be addressed later in the dopamine/dobutamine section of this article.

Epinephrine has been administered intravenously, endotracheally, and intraosseously. Because the efficacy of ET administration appears to be dependent on dose, patient (prehospital or hospital use), and technique, this route does not appear to be the preferred method for epinephrine administration.^{1,14,15,17,73-76} For epinephrine administration, the IOS route appears to be an excellent alternative to the IV route for the pediatric patient who may not have an IV line in place at the time of cardiac arrest or in whom starting an IV is difficult either peripherally or centrally.^{29,73} (See Table 1 for dosing information.)

SODIUM BICARBONATE

Inadequate ventilation in combination with poor tissue perfusion during cardiac arrest often results in a mixed respiratory and metabolic acidosis. Management of acidosis in this setting is an area of therapeutic controversy for those caring for pediatric patients.

In the past, sodium bicarbonate (NaHCO_3) was routinely administered for the correction of acidosis because bicarbonate is a physiologic buffer that can increase arterial pH. Current literature suggests that buffering occurs only when the carbon dioxide (CO_2) that is generated from bicarbonate's interaction with excess hydrogen ions can be adequately removed by the lungs.^{1,7,77} This situation presents a major problem for pediatric patients who experience cardiac arrest, because many of these infants and children have underlying pulmonary disease and experience respiratory failure prior to cardiac arrest.² These patients have a decreased ability to eliminate CO_2 , and administered bicarbonate has a propensity to transiently produce hypercapnia. Thus, because of their underlying pulmonary problems, intubation, effective ventilation, and adequate chest compression are more important for correcting acidosis and hypoxemia in these patients than is bicarbonate administration.^{1,7,77,78}

In metabolic acidosis associated with cardiac arrest, intramyocardial pCO_2 concentrations are elevated and intracellular pH is decreased. A similar process also occurs in the brain. Apparently, only adequate tissue perfusion can correct these problems.^{1,79} Bicarbonate administration without satisfactory ventilation and perfusion has been shown to worsen intracellular and cerebrospinal fluid acidosis. This deterioration occurs because CO_2 diffuses across cell membranes more rapidly than bicarbonate ions, and increased CO_2 cellular concentrations may lead to alterations in neurologic and myocardial function.^{1,7,77}

Maintaining adequate ventilation to combat acidosis has been demonstrated in newborn dogs. Steichen and Kleinman studied the effects of IV NaHCO_3 , on pH, PaCO_2 , and PaO_2 in 36 hypoxic, acidemic newborn dogs that were divided into four groups. Group I was hypoventilated with 100% O_2 and received NaHCO_3 , 2 mEq/kg IV over three minutes; Group II received NaHCO_3 in the same manner but was hypoventilated on room air; Group III received an equivalent dose of IV NaHCO_3 over three hours and was hypoventilated on room air; Group IV (control group) was hypoventilated on room air and received IV D5W instead of NaHCO_3 . Only animals in Group I maintained their pHs over the three-hour study period; the remainder dropped their pHs by 0.15–0.3 pH units (least reduction occurred in Group IV). Groups I and II experienced the greatest initial elevations in PaCO_2 , but then the PaCO_2 in Group I animals declined. Only Group II animals demonstrated a sudden fall in PaO_2 . The investigators concluded that when NaHCO_3 was administered to acidotic, hypoxic animals who were hypoventilated, a closed system was established in which CO_2 was retained.⁸⁰ The effect of bicarbonate in a closed system was most significant for Group II animals, but Group II and III animals had a more severe course than the controls. Group I animals, which were well oxygenated, had the best outcome, thus demonstrating the importance of maintaining adequate oxygenation to combat acidosis. Additionally, Jefferson et al. observed no difference in outcome of severely acidotic neonatal swine that received IV epinephrine and adequate ventilation versus those that received NaHCO_3 , 1 mEq/kg in addition to the previously mentioned treatment modalities.⁸¹

The routine use of NaHCO_3 is no longer recommended for pediatric patients who experience cardiac arrest.^{1,7,39,77} NaHCO_3 should only be administered after recommended

interventions including cardiac compression, ventilatory support, defibrillation, and epinephrine administration have been employed and the arrest is prolonged (>10 min).^{7,39} NaHCO_3 administration early in CPR may be beneficial in certain situations (e.g., patient has a preexisting acidosis), but such use should be individualized and not routine. Although controversial, NaHCO_3 administration also may benefit patients experiencing lactic acidosis.^{78,82,83}

Conversely, excessive bicarbonate administration can shift the oxyhemoglobin saturation curve to the left if metabolic alkalosis occurs, which can impair oxygen delivery to various tissues.¹ Bicarbonate has been shown to depress myocardial function, and cardiac arrhythmias may result from bicarbonate-induced alkalosis.⁷⁹ Serum potassium concentrations may be lowered as potassium is shifted intracellularly; ionized plasma calcium concentrations may be decreased, and serum sodium concentrations may be increased (because of the sodium content of the preparation).¹

Periventricular and intraventricular hemorrhages have been reported in immature neonates who received hyperosmolar bicarbonate solutions.^{77,84,85} Lou et al. have demonstrated that stressed neonates lose autoregulation of their cerebral blood flow.^{86–89} This leaves the immature cerebral perfusion and vasculature of the germinal matrix vulnerable to blood pressure fluctuations; the rapid infusion of NaHCO_3 has been reported to cause peripheral blood pressure fluctuations, decreased cerebral blood flow, and increased intracranial pressure in these patients. In addition, hypoxemia and CO_2 generated from NaHCO_3 administration may also dilate cerebral vessels.⁷⁷ Thus, the vasculature of the neonate appears to be more sensitive to bicarbonate therapy than the vasculature of adults. Therefore, if bicarbonate must be administered to a neonate, it should be given as a 0.5-mEq/mL (4.2%) solution or less. If only the NaHCO_3 , 1 mEq/mL (8.4%) solution is available, it should be diluted in sterile water for injection without preservatives prior to administration. D5W should not be used as a diluent because it would add to the osmolality of the solution.

Catecholamines can be inactivated by NaHCO_3 , and calcium salts will precipitate when mixed with NaHCO_3 .⁹⁰ To prevent these interactions, IV tubing used for drug administration should be flushed before and after bicarbonate administration, or separate IV lines should be used.

NaHCO_3 has been administered intravenously and intraosseously after the patient is appropriately ventilated and other CPR measures are being undertaken.¹ Animal studies have shown excellent response of study animals to IOS bicarbonate administration.^{86,91} In one of these studies, similar pH changes were demonstrated in approximately the same length of time after peripheral IV or IOS infusion.⁹¹ (See Table 1 for dosing recommendations.)

Not only are there controversies surrounding the use of NaHCO_3 for treating acidosis, but there also appears to be a controversy as to whether arterial blood gases should be used to monitor acidosis during CPR. This situation has arisen because there appears to be a disparity between arterial and mixed-venous pHs in animals and patients that have experienced cardiac arrest-associated acidosis.^{92–94} Venous pH may indicate an acidosis whereas an arterial blood sample reflects a normal pH or an alkalosis. This disparity may occur because arterial blood gases do not accurately reflect CO_2 accumulation in the pulmonary vasculature that

occurs when CO₂ is not adequately removed by the lungs. Additionally, mixed-venous blood gases may more accurately reflect tissue perfusion than arterial blood gases; they may represent a better way to monitor metabolic acidosis and its response to therapeutic interventions (including bicarbonate therapy).⁷⁹

Carbicarb (International Medication Systems), an experimentally used buffering agent that consists of an equimolar mixture of NaHCO₃ and disodium carbonate (Na₂CO₃), was formulated to raise blood pH without increasing CO₂ production and has been suggested as a possible alternative to NaHCO₃ in the treatment of metabolic acidosis.⁹⁵⁻⁹⁷ It was hoped that Carbicarb administration would elevate blood pH while intracellular pH increased, or at least did not decrease, as occurs when NaHCO₃ is administered for metabolic acidosis. Carbicarb also may be a more efficient alkalinizing agent than NaHCO₃ for an equal sodium load.⁹⁵⁻⁹⁷ It is more stable in solution than NaHCO₃ and loses CO₂ slowly when exposed to room air.⁹⁸ Additionally, Carbicarb has the capacity to generate bicarbonate ions not only from carbonate ion when added to blood but from CO₂ in the blood or poorly perfused tissues that may be reservoirs for CO₂.

To date, only animal studies have been performed that address the potential usefulness of Carbicarb in treating acidosis. The results from studies where various rat models for systemic acidosis or lactic acidosis were used have shown that Carbicarb administration can increase systemic and brain pH without increasing blood pCO₂, when compared with NaHCO₃ administration, which resulted in decreased brain pH and increased blood pCO₂, while producing a systemic alkalosis.^{95,96} Similar arterial pH and pCO₂ results were reported by Sun et al.⁹⁹ Bersin and Arieff, using a canine model in which animals were made acidotic by administration of a hypoxic gas mixture, reported improvements in arterial and liver pHs as well as in hemodynamic and cardiac function following Carbicarb administration, whereas the opposite occurred after bicarbonate administration.¹⁰⁰ Kindig et al. noted that the administration of Carbicarb or NaHCO₃ to dogs made acidotic with hydrochloric acid infusions resulted in systemic alkalization, but only Carbicarb administration did not increase CO₂ generation.¹⁰¹

Although the previously discussed studies have shown promising results from Carbicarb administration,^{95,96,99-101} studies using either a swine or canine CPR model have not shown similar benefits.^{97,102,103} In one study, both Carbicarb and NaHCO₃ increased the systemic pH but not intramyocardial pH in swine that had been subjected to ventricular fibrillation. The administration of the buffers (as well as hypertonic saline used as a control) did not improve myocardial acidosis nor did the administration of any of the three agents improve myocardial resuscitability.¹⁰² In a second swine study, 25 miniature swine received Carbicarb, NaHCO₃, or a sodium chloride solution (used as a control) after ventricular fibrillation was induced. Both buffers significantly increased the pH and bicarbonate concentrations of arterial, mixed-venous, and coronary vein blood, but only Carbicarb administration resulted in a decreased systemic blood PCO₂. Neither buffer, however, decreased PCO₂ or lactate content in the coronary veins. Additionally, resuscitability was no better in animals that received Carbicarb (5/8 successfully resuscitated) than in those adminis-

tered NaHCO₃ (4/8) or those in the control group (6/9).¹⁰³ Bleic et al. compared the effects of NaHCO₃, Carbicarb, and dextrose administration using a canine ventricular fibrillation and cardiopulmonary resuscitation model. All dogs underwent ventricular fibrillation three times and were treated after each episode with epinephrine and one of the three agents being tested. Bicarbonate, Carbicarb, and dextrose were administered in a random order to all dogs so that each dog served as its own control. There was no significant difference in the time to recovery (15 min and 20 ± 30 s after bicarbonate administration, 16 min and 23 ± 43 s after Carbicarb, and 14 min and 2 ± 57 s after dextrose) or the recovery rates after ventricular fibrillation among the agents used (8/13 after bicarbonate administration, 10/14 after Carbicarb, and 9/11 after dextrose).⁹⁷

Although some studies have shown promise for Carbicarb administration in the treatment of acidosis, recent animal studies using ventricular fibrillation and CPR models have not shown Carbicarb to be more effective than NaHCO₃. Additional animal studies or prospective studies in humans undergoing CPR are needed before Carbicarb's efficacy in the treatment of CPR-related acidosis can be definitely determined.

ATROPINE

Atropine is indicated for the treatment of bradyarrhythmias and asystole. Through its parasympatholytic action, atropine increases activity of the sinoatrial node and atrioventricular conduction. Low doses, however, may cause a paradoxical parasympathomimetic action that may further depress automaticity and conduction.¹⁰⁴

Atropine may be useful in the treatment of pediatric patients who experience bradyarrhythmia with poor perfusion, hypotension, or asystole. Atropine also may be used to counteract vagally induced bradyarrhythmia sometimes produced by attempted intubation. In distressed but normotensive infants less than six months of age where cardiac output is dependent upon heart rate, bradyarrhythmia (rate < 80 beats/min) should be treated.⁷

Because bradyarrhythmia can result from hypoxemia, providing adequate ventilation should precede atropine use. When atropine is deemed necessary, doses of 0.02 mg/kg can be administered by the IV, IOS, or ET route (see Table 1 for further dosing information). A minimum dose of 0.1 mg should be used to avoid the paradoxical bradycardic effect. Maximum single doses or cumulative total doses (0.02 mg/kg repeated q5min) of 1 mg in children and 2 mg in adolescents should be used.⁷ Although tachycardia may accompany atropine use, significant adverse hemodynamic effects are usually absent.

CALCIUM

Calcium is no longer recommended in the ACLS or APLS guidelines for CPR resulting from asystole or electromechanical dissociation (EMD).^{7,9} This change from those recommendations previously published¹⁰⁵ occurred because data supporting the use of calcium to reestablish cardiac function following asystole are lacking; its use for EMD is questionable.¹⁰⁶⁻¹⁰⁹ Furthermore, adverse effects associated with excessive calcium administration have been documented.^{110,111} To date, no data are available that specifically address the benefits of calcium in pediatric CPR or

the safety of calcium doses that have been used during pediatric CPR.³

Several studies have addressed the efficacy of IV calcium chloride (CaCl₂) administered to adults who experienced cardiac arrest secondary to asystole, EMD, or ventricular fibrillation. Stueven et al. studied 210 prehospital adult cardiac-arrest victims (129 diagnosed as having asystole and 81 with EMD). Eight of 105 who received IV CaCl₂ for asystole (8 percent) were successfully resuscitated whereas 8 of 24 (33 percent) who did not receive calcium were also resuscitated. Of the 63 patients who received calcium for EMD, 16 percent were resuscitated; 44 percent of those who did not receive calcium were resuscitated. None of the 168 patients who received calcium were discharged from the hospital whereas five who did not receive calcium were discharged.¹⁰⁶

In an uncontrolled study of 480 adult patients who experienced EMD, ventricular fibrillation, or asystole, a response to calcium therapy was observed in 27 patients. These patients received a mean dose of CaCl₂ 900 mg as well as NaHCO₃ and epinephrine. Only three responders lived to be discharged.¹⁰⁷

Seventy-three adults with asystole refractory to epinephrine, NaHCO₃, and atropine were enrolled in a prospective, randomized, blind study to compare the effectiveness of IV CaCl₂ with saline. Of 39 patients who received calcium, three were successfully resuscitated; one patient out of 34 in the saline group was resuscitated. None of those resuscitated was discharged.¹⁰⁸

A prospective, randomized, blind study was performed to compare CaCl₂ with IV saline in the resuscitation of adults experiencing EMD in the prehospital setting. All patients received NaHCO₃ and epinephrine and were considered refractory to therapy before randomization into the CaCl₂ or the saline group. Those in the calcium group each received CaCl₂ 500 mg. Eight of 48 patients in the calcium group were successfully resuscitated, but only one was discharged from the hospital. Two of 42 in the saline group were successfully resuscitated, but neither left the hospital. Although there was a statistical difference between response to CaCl₂ versus saline ($p \leq 0.028$), there was no difference in mortality.¹⁰⁹

Calcium is indicated for hypocalcemia, hyperkalemia, hypermagnesemia, and for calcium channel-blocker overdose.¹⁷ For these indications, CaCl₂ is the preferred salt because there is more physiologically active ionic calcium available.¹¹² (See Table 1 for dosing information.)

DOPAMINE/DOBUTAMINE

Dopamine and dobutamine are catecholamines useful in the postarrest setting to enhance myocardial contractility and peripheral vascular resistance once circulation has been restored and respiration supported. Dopamine produces variable pharmacodynamic responses based upon the dose used. With infusion rates of 5–15 µg/kg/min, enhanced contractility and heart rate primarily occur through stimulation of beta₁-receptors. Alpha-adrenergic stimulation begins to predominate at infusion rates between 10 and 15 µg/kg/min, which causes peripheral vasoconstriction supporting blood pressure.²⁴ Dopamine is used routinely for cardiovascular support in pediatric patients of all ages, including neonates.^{24,113–115} Because dopamine phar-

macology is complex and the point at which various receptor populations are stimulated may vary in individual patients, dopamine infusions must be titrated to individual response. Adverse effects that may appear at higher doses include tachycardia, hypertension, and ventricular arrhythmias. Guller et al. retrospectively reviewed experiences with dopamine in 31 children. Six of the 31 developed arrhythmias associated with dopamine infusions in excess of 10 µg/kg/min; however, doses as high as 75 µg/kg/min were used without associated rhythm disturbances.¹¹⁶ Caution must be exercised in patients with preexisting pulmonary hypertension because this condition may be exacerbated.¹¹⁷ Administration of dopamine is best done using central IV access, as infiltration of peripheral lines may result in significant extravasation and tissue damage.^{8,118}

There is little information about using dopamine for the initial treatment of cardiac arrest. High doses of dopamine (40 mg) administered to dogs weighing 12–20 kg produced a return of circulation in 90 percent or more of the animals that had undergone either asphyxial or fibrillatory arrest. These results were similar to those noted for animals that received doses of epinephrine 1 mg, but animals in a third group that received dobutamine 50 mg demonstrated poor recovery (only 2/10 in either the asphyxia group or the fibrillation group survived).¹¹⁹ In another study, the effectiveness of dopamine 2.5 mg/kg was compared with epinephrine 45 µg/kg and no drug therapy (control group) after either asphyxial arrest or ventricular fibrillation in swine. Resuscitation of the animals in the asphyxial arrest group was better after epinephrine administration with all seven animals surviving, whereas only three of the seven in the dopamine group and none in the control group survived. Results were different in the ventricular fibrillation animals; all animals receiving dopamine were resuscitated and in a shorter time period than those that received epinephrine. The authors theorized that animals in the ventricular fibrillation group were resuscitated more quickly after dopamine administration because dopamine may penetrate the sympathetic nerve endings and release stored norepinephrine.¹²⁰ Gonzalez et al. prospectively enrolled nine patients who had not responded to standard ACLS therapy into a group (n=5) that would receive increasing IV doses of epinephrine (1, 3, and 5 mg) or into a group (n=4) that would receive dopamine (15 µg/kg/min) in addition to the epinephrine dosing.¹²¹ Dose-related increases in peak systolic blood pressure were noted for patients in the epinephrine-only group but were not observed in the epinephrine-dopamine group. The investigators stated that the administration of epinephrine alone appears to produce "a dose-dependent vasopressor response during CPR in humans," but patients receiving high doses of epinephrine and dopamine do not receive an additive vasopressor effect.¹²¹

Dobutamine exhibits relatively selective beta₁-adrenergic activity, therefore increasing myocardial contractility and cardiac output, primarily caused by an increased stroke volume.¹²² Heart rate is mildly increased and blood pressure may increase, decrease, or remain unchanged. In contrast to dopamine, dobutamine acts directly on receptors and does not rely on the release of endogenous catecholamine stores. Little published information regarding dobutamine's effect in pediatric patients is available. Most of the guidelines for use are extrapolated from adult studies. Pediatric studies show dobutamine to be an effective ino-

tropic agent with variable responses in heart rate, systemic vascular resistance, and pulmonary capillary wedge pressure. In a group of 33 patients aged 4 weeks to 17 years who had either cardiogenic shock or septic shock, Perkin et al. measured hemodynamic responses to dobutamine. As expected, the cardiac index increased with stepwise increases in dose when compared with preinfusion values. Those with cardiogenic shock exhibited greater increases in the cardiac index; however, the difference was not statistically significant. In the subgroup of patients less than 12 months of age (n=10), the cardiac index did show stepwise increases over baseline ranging from 7 to 18 percent; however, it did not reach statistical significance. Pulmonary wedge pressure did show stepwise increases in this same subgroup and reached statistical significance at the 10 $\mu\text{g}/\text{kg}/\text{min}$ infusion rate. The most common adverse effects observed were arrhythmias, systemic hypertension, and pulmonary edema secondary to increased pulmonary wedge pressure. A decrease in infusion rate resulted in resolution of symptoms.¹²³ Schranz et al. also found significant chronotropic effects in pediatric patients receiving infusions of 7.5–10 $\mu\text{g}/\text{kg}/\text{min}$.¹²² Cardiac output increased in all patients, including those less than 12 months of age (n=6). Clinically, dobutamine may prove useful in low-cardiac output syndromes in all age groups; however, caution should be exercised in preexisting pulmonary hypertension. The general scheme of dosing titration follows that of dopamine with an initial infusion of 5–10 $\mu\text{g}/\text{kg}/\text{min}$, up to 20 $\mu\text{g}/\text{kg}/\text{min}$ according to patient response.⁷ Rates in excess of 20 $\mu\text{g}/\text{kg}/\text{min}$ are generally of no further benefit, and adverse effects such as hypertension, tachycardia, and arrhythmias may increase.¹¹⁶

Although dopamine and dobutamine both have been used successfully in neonates and infants, some controversy exists regarding the preferred agent for this group. Fetal and neonatal animal studies have demonstrated immature myocardial adrenergic innervation, reduced norepinephrine stores, reduced norepinephrine uptake and storage capacity, and increased beta-receptor sensitivity.^{124–127} Because of variability in the maturation of myocardial adrenergic innervation and renal dopaminergic receptor mass, dose-response relationships may be altered when compared with those of older children and adults.¹¹⁴ Dopamine has been noted to have decreased efficacy in longstanding congestive heart failure or in young infants.¹²⁸ Therefore, because dopamine's inotropic effects depend in part upon indirect release of norepinephrine in the myocardium, direct agonists may in some instances be preferred.¹²⁷ The reader is referred to two articles reviewing this subject in detail.^{129,130}

LIDOCAINE

Lidocaine, structurally similar to local anesthetics, exerts its antiarrhythmic effect by suppressing automaticity and spontaneous ventricular depolarization during diastole. Although the need to use lidocaine is infrequent in the pediatric population, it is indicated for ventricular tachycardia or fibrillation. It also is indicated in hemodynamic compromise accompanied by ventricular arrhythmias, such as frequent ventricular premature beats, and other malignant ventricular rhythms.⁷ Bolus doses of 1 mg/kg may be administered by the IV, IOS, or ET route (see Table 1) and may be repeated twice at intervals of 5–15 minutes if necessary.^{7,24}

Additionally, a lidocaine infusion of 20–50 $\mu\text{g}/\text{kg}/\text{min}$ may be started to maintain therapeutic concentrations.^{1,7,24} Infusion rates may need to be decreased in situations resulting in decreased hepatic blood flow or function, such as shock, cardiac dysfunction, and known liver disease when lidocaine clearance is decreased.¹³¹ Lidocaine toxicity is manifested primarily as central nervous system abnormalities, such as drowsiness, disorientation, and even seizures that may result when infusion rates are in excess of clearance rates. Lidocaine concentrations, therefore, should be monitored closely. Serum lidocaine concentrations of 2–5 $\mu\text{g}/\text{mL}$ generally are associated with efficacy and minimal toxicity. Concentrations above 6 $\mu\text{g}/\text{mL}$ generally are associated with significant risks of both central nervous system and cardiac toxicity. If signs of significant toxicity appear, particularly if early in the course of therapy, the infusion should be temporarily stopped and then restarted at a lower rate to avoid significant drug accumulation.

BRETYLIUM

Although there is little published experience with bretylium in the pediatric patient, and it does not hold the preferred status over lidocaine as it does in the adult population, it may prove useful in cases of failure with lidocaine. Bretylium, a Class III antiarrhythmic agent, has a mechanism of action unlike that of lidocaine and the Class I antiarrhythmic agents. Following uptake by the adrenergic nerve endings, bretylium has a biphasic effect on the sympathetic nervous system.^{132,133} Initially, catecholamine release occurs, which may cause transient increases in myocardial contractility and blood pressure. Secondly, catecholamine release is inhibited, thereby increasing the ventricular fibrillation threshold. Significant hypotension may also occur secondary to sympatholytic activity; therefore, patients should be closely monitored. Published guidelines for the use of bretylium in pediatric patients suggest an initial dose of 5 mg/kg IV followed by a defibrillation attempt. If this attempt is unsuccessful, the dose may be increased to 10 mg/kg followed by another attempt at electrical defibrillation.^{1,7,24,134,135} The ET administration of bretylium was evaluated in the canine model, but was found to be ineffective in doses as high as 20 mg/kg despite the use of a device designed to ensure site-specific delivery.¹³⁶

NALOXONE

For completeness, information regarding naloxone use is included here. Naloxone, a pure narcotic antagonist, is the drug of choice for treatment of cardiorespiratory depression associated with narcotic agonists. It has been used successfully in the pediatric population to reverse neonatal respiratory depression caused by intrapartum administration of narcotics, manage pharmacologic narcotic excess, and treat accidental narcotic ingestions. The recommended dose is 0.1 mg/kg IV or ET from birth to 5 years of age or up to a weight of 20 kg. A minimum of 2 mg should be used beyond this point.¹³⁷ Pharmacokinetic studies in neonates reveal mean plasma half lives of 3.1 ± 0.5 h in full-term infants after either a 35- μg or 70- μg dose given by umbilical vein¹³⁸ and 1.2 ± 0.6 h in a group of 10 premature neonates receiving 40 $\mu\text{g}/\text{kg}$ IV, despite immature glucuronidating capability in this patient population.¹³⁹ Time to peak serum concentrations varied from 5 to 40 minutes

depending at least in part on route of administration.^{138,139} The minimum effective dose may need to be repeated when narcotic metabolism is significantly slower than naloxone's, which would allow narcotic-induced cardiorespiratory depression to return.^{140,141} Caution must be exercised in the use of naloxone in the newborn, as indiscriminate use in infants of narcotic abusers may precipitate withdrawal in these infants.^{142,143} Naloxone is available in 0.02-mg/mL (neonatal), 0.4-mg/mL, and 1-mg/mL strengths. Because of the large fluid volumes that may be required to provide doses of 0.1 mg/kg, the use of the neonatal preparation is no longer recommended, particularly for small neonates.¹³⁷ Moore and Rumack recommend an initial trial dose of 0.01 mg/kg followed two minutes later by 0.1 mg/kg if no clinical response is seen.¹⁴⁴ Alternatively, a continuous infusion may be used, particularly in cases of significant overdose.¹⁴⁵⁻¹⁴⁸

Summary

Pediatric cardiorespiratory arrest results in high morbidity and mortality rates. Because of fundamental differences between adult and pediatric patients in the usual origin of arrest, likelihood of arrhythmias, difficulty in securing IV access, and the varying responses to CPR drugs, the approach to managing the pediatric patient may also be different. Advances have been made in gaining IV access, using the ET route for drug administration and, once again, using the IOS route for drug therapy. Optimal doses, however, still need to be identified for the ET route.

Providing adequate ventilation is crucial in the pediatric patient, as respiratory insufficiency is often the primary cause of arrest. Epinephrine remains the initial drug of choice in attempts to restore circulation and may be readily administered by the ET route as well as by the IV and IOS routes. Epinephrine dosage selection, however, remains controversial at this time. NaHCO₃ use has been limited by revised guidelines, and the indications for calcium administration are few. Atropine must be used in adequate doses to prevent paradoxical parasympathomimetic activity when it is needed for bradyarrhythmias or asystole. Postresuscitation support is largely accomplished with catecholamine infusions. The choice of catecholamine is primarily dependent on the hemodynamics of the individual patient. For those few situations calling for an antiarrhythmic agent, lidocaine remains the first-line agent, and as experience with bretylium in the pediatric patient increases, the indications for its use may change. ≡

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EXTRACTO

En este artículo se discuten algunas controversias terapéuticas acerca de los fármacos que podrían ser necesarios durante la resuscitación cardiopulmonar (RCP) pediátrica y las rutas de administración que pueden ser seleccionadas. Entre las controversias discutidas se incluyen: la elección apropiada de varias rutas de administración durante RCP, determinando si epinefrina es el agente adrenérgico de elección para RCP y su dosis apropiada; tratamiento de acidosis asociada con arresto cardiopulmonar; recomendaciones de las dosis de atropina y el rol de

The Guide to Cardiology

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Cardiopulmonary Resuscitation

Although resuscitation has been performed for thousands of years, only in the last century has it been performed with any measure of success. Despite reports of success with external chest compression and artificial ventilation in the late nineteenth century, direct internal cardiac massage remained the standard mode of resuscitation until the value of external chest compression was redescribed in 1960. Basic cardiopulmonary resuscitation has changed little since then.

Each year, more than 500,000 people die suddenly from cardiac causes in the United States. Prompt institution of resuscitative efforts could save many of these lives. Reported success rates for cardiopulmonary resuscitation vary from 10% to 90%. In general, the success rate is low among critically ill patients and when institution of resuscitation is delayed; the success rate is high among patients in whom primary ventricular fibrillation is rapidly identified and treated. In out-of-hospital victims of ventricular fibrillation, resuscitation is successful less than 40% of the time.

External chest compression and mouth-to-mouth ventilation are temporizing measures, designed to prevent irreversible ischemic deterioration while the patient awaits more definitive therapy. Although no absolute rules predict the success of resuscitation, the success rate is very low if basic resuscitation is instituted beyond 4 to 5 minutes. If more advanced resuscitative efforts are delayed by 7 to 8 minutes, chances of survival are even lower. In certain causes of cardiac arrest, particularly hypothermia, these guidelines do not apply and patients may be successfully revived after much longer delays. In general, how-

ever, time is the most important predictor of successful resuscitation.

Causes of Cardiac Arrest

The most common causes of sudden death are ventricular tachycardia and ventricular fibrillation. Other tachyarrhythmias, such as atrial fibrillation in the patient with accelerated atrioventricular conduction, may occasionally cause sudden death. Bradyarrhythmias are less common precipitating events; ischemia-induced sinus arrest or complete heart block are the usual causes.

Other causes of sudden death include primary respiratory arrest; electromechanical dissociation (absence of effective mechanical systole despite persistent electrical complexes); and acute mechanical lesions, such as massive pulmonary embolism, acute disruption of the cardiac valves or great vessels, pericardial tamponade, and myocardial rupture. Regardless of the cause of cardiac arrest, the initial approach to the victim is the same.

Mechanisms of Blood Flow During Resuscitation

The success of cardiopulmonary resuscitation depends in large part on achieving adequate blood flow to the heart and brain. External chest compression was initially described as "closed-chest cardiac massage," implying that resuscitation-induced blood flow was a result of the heart being squeezed between the sternum and spine, mimicking the action of internal cardiac compression and propelling blood forward by increasing the intracardiac pressure above the aortic pressure. However, recent work by many investigators casts doubt on the validity of this proposed mechanism. It is now apparent that cardiac output during sternal compression may be due at least in part to an increase in intrathoracic pressure during each compression. According to this hypothesis, the heart acts as a

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conduit for blood flow rather than as a pump. When intrathoracic pressure is elevated by chest compression, blood is squeezed out of the thorax. Retrograde flow is prevented by the cardiac and systemic venous valves, and possibly by collapse of the systemic veins as they exit from the thorax. Thus, as intrathoracic pressure rises, blood is forced from the lungs through the heart and into the aorta. As pressure on the sternum is released, blood flows back into the pulmonary vascular bed from the systemic veins. Flow from the aorta back into the heart is prevented by the aortic valve.

Evidence for such a flow pattern was originally based on clinical observations. Patients with flail chests, in whom the unstable chest segment precludes the attainment of a positive intrathoracic pressure with sternal compression, were at times revived only after stabilization of the chest wall. Emphysematous patients were not more difficult to resuscitate despite the increased distance between their sternum and spine. Coughing, which substantially increases intrathoracic pressure, was noted to generate remarkable cardiac output in the absence of cardiac systole; in fact, repetitive coughing maintains consciousness in humans with ventricular fibrillation. Recent attempts to duplicate the physiology of the cough by increasing abdominal pressure (with binding, for example) and by inflating the lungs simultaneously with sternal compression have resulted in demonstrable increases in forward blood flow during resuscitation.

Hemodynamic data also support a role for the "chest pump" hypothesis. Measured pressures in the great vessels and intracardiac chambers can be equal during sternal compression; if forward blood flow were due to direct squeezing of the heart, intracardiac pressures should exceed pressures elsewhere in the thorax. In addition, angiographic and two-dimensional echocardiographic views show that some patients exhibit flow through open mitral and aortic valves during sternal compression. However, some investigators have reported evidence for direct cardiac compression, during resuscitation, at least in dogs. In some patients, either or both proposed mechanisms of flow could occur.

Supplemental maneuvers, such as abdominal binding, interposed abdominal compression, and simultaneous lung inflation with chest compression can further increase intrathoracic pressure and carotid blood flow during sternal compression, according to some studies. Recent studies in animals and humans indicate potentially better survival with interposed abdominal counterpulsation during cardiopulmonary resuscitation, but optimal use of this technique has not been fully demonstrated.

Technique of Cardiopulmonary Resuscitation

Figure 1 is a diagram of the process of cardiopulmonary resuscitation.

Ventilation. Once a patient is determined to have had a cardiac arrest, a patent airway must be established. This is accomplished most quickly by placing the patient in the

supine position and tilting the head back while simultaneously pulling the jaw forward and opening the mouth slightly. These maneuvers preclude airway obstruction by the tongue and pharynx, and allow inspection of the pharynx if ventilatory difficulties indicate upper-airway obstruction.

Mouth-to-mouth resuscitation at a rate of about 12 breaths/min can then be instituted. Adequate ventilation may be gauged by the presence of chest expansion and the sounds of the victim's exhalations. Mouth-to-mouth ventilation is a temporizing measure, as the fractional inspired oxygen so administered is only 0.17. In a prolonged resuscitation, this will usually be insufficient to achieve adequate arterial oxygenation. Therefore, the use of a respirator bag and a tight-fitting mask, esophageal airway, or endotracheal tube is necessary to administer 100% oxygen if initial attempts at restoring spontaneous ventilation are unsuccessful. Endotracheal intubation also provides a route for drug administration if intravenous cannulation is unavailable.

The adequacy of ventilation should be monitored by arterial blood-gas determinations. Hyperventilation is frequently necessary to compensate for the metabolic acidosis often seen in the patient with cardiac arrest. The arterial pH should be maintained at 7.30 to 7.45. Hypoxia is invariably present because of intrapulmonary shunting; therefore, 100% oxygen should always be administered. Use of high levels of oxygen for brief periods is not dangerous.

Arterial blood-gas levels are poor indicators of tissue acid-base status and oxygenation during resuscitation, but are necessary to assess the adequacy of ventilation and pulmonary gas exchange, although mixed venous blood gas levels and end-tidal carbon dioxide levels are much better measures of tissue perfusion. This disparity is due to the poor cardiac output achieved during resuscitation. Such low flow leads to poor delivery of carbon dioxide to the lungs, with a resultant striking degree of hypercapnia and acidosis in the tissues and in venous blood. In such situations, arterial blood gas measurements give insufficient and potentially misleading information about the adequacy of tissue perfusion, and usually mask the severity of tissue ischemia.

Upper-airway obstruction due to foreign body aspiration, as in the so-called "caf  coronary syndrome" caused by the aspiration of food, may be treated successfully by use of the Heimlich maneuver. The rescuer stands behind the victim with the fists clenched beneath the victim's xiphoid process, and delivers a swift thrust upward and inward. This usually drives the diaphragm up and expels the blocking agent from the airway.

Circulation. Adequate circulation must be achieved simultaneously with the restoration of effective ventilation. External chest compression usually produces 25% or less of the normal cardiac output. This reduced output is directed predominantly cephalad and is often sufficient to perfuse the brain, at least temporarily. Myocardial perfusion is much less optimal. Coronary blood flow during resuscitation may be less than 10% of normal. Insufficient myocardial blood flow is frequently the cause of inability to achieve a stable cardiac rhythm. This suboptimal flow is due to the low diastolic blood pressure (and thus a poor

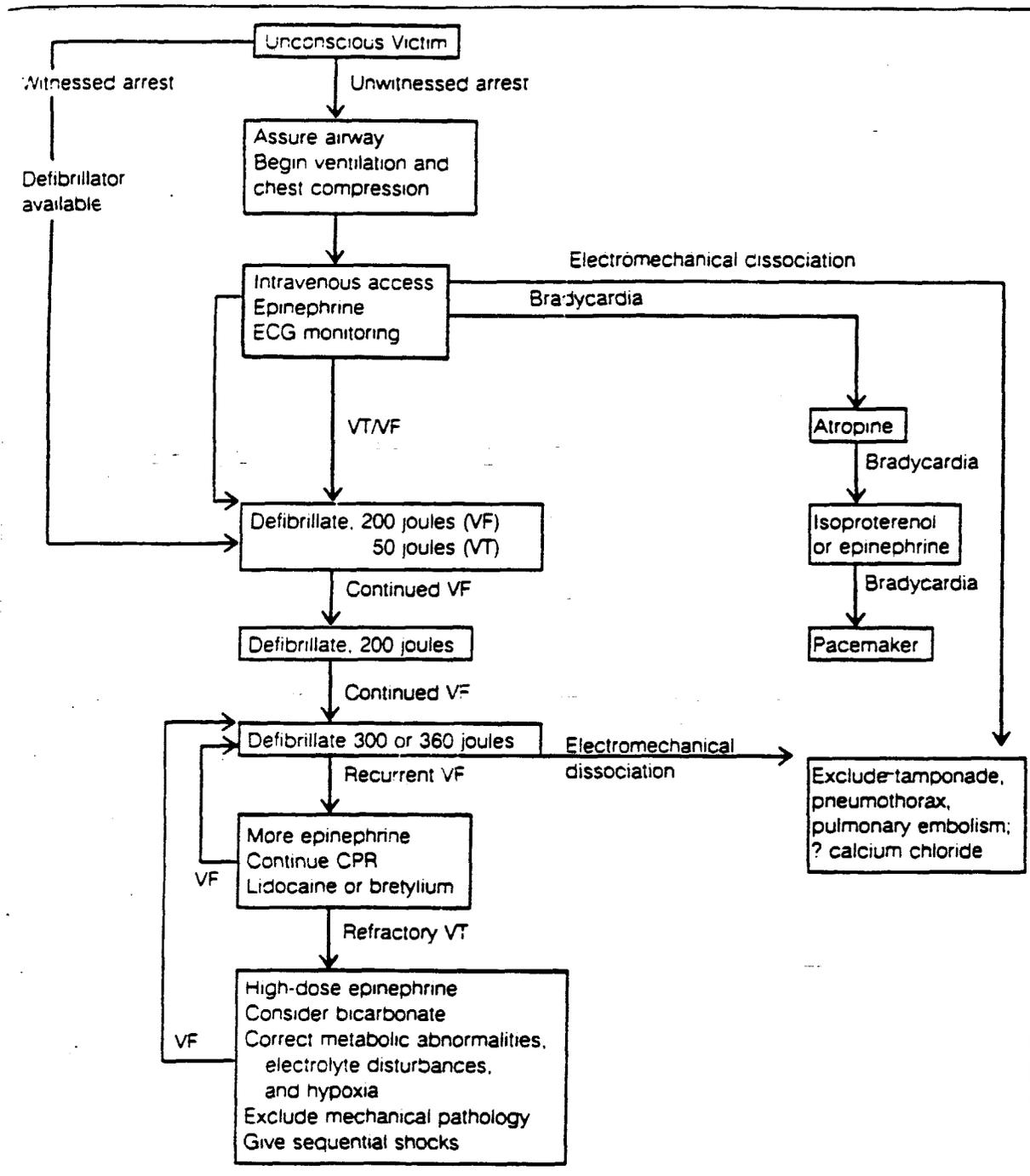


Figure 1. The steps instituted during a typical cardiopulmonary resuscitation. If the electrocardiogram reveals ventricular tachycardia, a chest thump may be attempted. See text for further discussion of the use of the chest thump, and for dosages and dosing intervals of the various treatment agents named in the figure.

driving force for coronary artery perfusion) attained during resuscitation.

Proper chest compression is important for maximizing blood flow during resuscitation. The rescuer kneels or stands beside the victim and places his or her interlocked hands, one atop the other, on the lower half of the victim's sternum. The exact position is not critical as long as the hands are above the xiphoid process (pressure on the

xiphoid may result in ineffective thoracic compression and/or hepatic lacerations). If sternal placement of the hands is impossible, positioning of the hands anywhere on the thorax can be effective. For instance, one hand can be placed on each hemithorax. Each compression is accomplished by depressing the sternum by 4 to 6 cm. This is most easily done by locking the elbows and leaning over the victim's chest, thereby transmitting the weight of the

upper torso to the hands. A force of 60 to 90 pounds is usually needed. A firm surface beneath the patient makes the job easier and more effective, but successful compressions can be performed with a patient in bed, if necessary.

The optimal rate, force, and velocity of chest compressions are controversial. Although early observers noted no significant change in blood flow with rates of 40 to 120 compressions/min, more recent reports indicate a rise in output over this range. For this reason, a rate of 80 to 120 compressions/min is recommended. The duration of compressions may be important: 50% to 60% "downtime" results in improved flow than do briefer periods of compression during slow rates, but this variable appears to be less important at faster compression rates. Recent data show that "high impulse" compression, in which the velocity of initial chest compression is increased, achieves higher systolic and diastolic pressures, and superior myocardial and cerebral perfusion. Chest compression force is also an important variable: increased force results in a higher cardiac output. Ventilations should be interposed between every fourth or fifth compression, if a rescuer is alone, this pattern can be modified so that two ventilations are administered between every 12 to 15 compressions. In sum, a regimen of 80 to 120 forceful, high-velocity compressions per minute is recommended.

Internal cardiac massage results in demonstrably better cardiac output than sternal compression, but is used infrequently because it is an invasive technique. Nevertheless, it is indicated in certain cases of penetrating cardiac trauma; in the postoperative cardiac surgical patient; in mechanical lesions such as aortic stenosis, in the patient with a grossly unstable chest; in some patients with prosthetic valves (external pressure applied over prosthetic valve rings may cause cardiac trauma during chest compression); and in patients who have failed to respond to more routine measures.

The precordial thump has a low success rate and is therefore no longer recommended in the unwitnessed arrest. It may be useful for the patient with witnessed ventricular tachycardia, in which a single thump may convert the patient to sinus rhythm, or the patient with severe bradycardia, in which repetitive thumps may induce spontaneous cardiac contractions. From a height of 20 to 30 cm above the victim's chest, the fleshy portion of the fist is used to deliver a swift blow to the midsternum. Conscious patients will not like this maneuver, and alternative modes of therapy, such as intravenous lidocaine for the patient with ventricular tachycardia, should be considered.

Electrical Cardioversion and Defibrillation

Direct-current electrical defibrillation is by far the most useful element in successful cardiopulmonary resuscitation. When instituted promptly, it has a very high success rate in a variety of dysrhythmias. Defibrillators deliver a monophasic depolarization of several thousand volts over a period of about 10 msec. The delivered energy can be varied up to a maximum of 360 joules (watt-seconds) on most defibrillators.

The optimal power setting for external cardiac defibrillation has been debated. Advocates of high-energy shocks maintain that body weight is a variable in determining the power requirements for successful defibrillation, but this has not been borne out by clinical studies. High-energy shocks result in increased electrical injury to the myocardium and a higher incidence of post-shock asystole and atrioventricular block. Current evidence indicates that 200 joules is optimal for initial attempts at defibrillation; much less energy (10–50 joules) is usually required for the conversion of ventricular tachycardia.

The technique of defibrillation is straightforward. The machine is set to the desired power level and the paddles are charged. Exact paddle placement is less critical than ensuring that adequate electrode paste (or saline pads) and firm paddle pressure are used, since these simple maneuvers will maximize the amount of energy delivered to the victim. One paddle is placed just below the right clavicle; the other is placed just lateral to the cardiac apex (or below the left scapula, when a flat posterior paddle is used). When everyone stands clear of the patient and the bed, the shock is delivered. Additional shocks of 200 to 360 joules are administered if needed, usually in prompt succession.

In the monitored patient with witnessed ventricular tachycardia or ventricular fibrillation, electrical therapy, if immediately available, must not await the initiation of chest compression and ventilation. There is no reason to delay delivery of the definitive treatment for these arrhythmias. In the unwitnessed arrest, cardiopulmonary resuscitation and pharmacologic intervention are often used for 1 to 2 minutes before countershock is attempted. This may increase the likelihood of successful conversion; however, even in an unwitnessed arrest a rapidly administered shock may be lifesaving and must be delivered as soon as possible.

Some patients have recovered even after several hours of ventricular fibrillation and cardiopulmonary resuscitation; therefore, attempts at defibrillation should continue until irreversible cardiac asystole appears. If several attempts at defibrillation fail, more intensive pharmacologic therapy, closer attention to metabolic abnormalities, and higher-energy shocks may be useful. Rapid sequential shocks, spaced a few seconds apart, are occasionally beneficial, since the first shock lowers skin impedance and allows a higher delivery of energy by the second shock.

Asystole has the poorest prognosis of any arrhythmia and is rarely responsive to cardioversion. Although successful shocks have been reported in cases of asystole, ventricular fibrillation was probably present in these patients. If asystole appears on the electrocardiographic monitor, the monitor's gain should be increased and the electrical leads should be changed to obtain a configuration perpendicular to the first lead. This ensures that the tracing is not actually ventricular fibrillation, which occasionally may be isoelectric in a particular lead.

Pharmacology of Resuscitation

Effective restoration of circulation often depends on pharmacologic manipulation (Table I). Rapid placement of an

TABLE I: DRUGS FREQUENTLY USED DURING CARDIOPULMONARY RESUSCITATION

| DRUGS | DOSE | ROUTE | MECHANISM OF ACTION | COMMENTS AND PRECAUTIONS |
|--------------------|--|------------|--|---|
| Epinephrine | ≥ 1.0 mg every 5 minutes or continuous infusion (1 ampule = 1 mg) | IV, ET, IC | Increases blood pressure and heart rate | Drug of choice for resuscitation; inactivated by sodium bicarbonate |
| Sodium bicarbonate | After initial 5-10 minutes, 1 mEq/kg, then 0.5 mEq/kg as needed (1 amp = 44.6 or 50 mEq) | IV | ? Helps prevent acidosis | May result in alkalemia, hypernatremia, hyperosmolar state; inactivates epinephrine; precipitates with calcium |
| Calcium chloride | 250-1,000 mg (1 amp = 1 g) | IV, IC | Increases contractility (?) Helps electromechanical dissociation | Precise role undefined. Intracardiac injection may cause severe bradycardia; precipitates with bicarbonate; contraindicated in digitalis toxicity |
| Atropine | 0.5-1.0 mg every 5 minutes up to 3 mg (1 amp = 1 mg) | IV, ET, IC | May reverse bradycardia or heart block | Low doses may cause paradoxical bradycardia |
| Lidocaine | 100-300 mg in 50-100 mg boluses; then 1-4 mg/min | | May prevent ventricular fibrillation | High doses may cause central nervous system toxicity |
| Bretylium | 5 mg/kg every 10 minutes up to 30 mg/kg; then 1-2 mg/min | | May prevent or convert ventricular fibrillation; lowers threshold for successful cardioversion | Can cause hypotension |

IV = intravenous; ET = endotracheal route; IC = intracardiac.

intravenous line is crucial. Any vein can be used, but a vein above the diaphragm is preferred. Blood flow during chest compression may be preferentially directed cephalad; infusion into the saphenous or femoral veins may therefore result in delayed entry of instilled medications into the central circulation. If an arm vein is palpable, it should be used, although this is often impossible because of the marked venospasm that may accompany cardiac arrest. In this situation the external or internal jugular vein should be cannulated. The subclavian vein may also be used, but this approach carries a higher incidence of potentially serious complications, and the vein may be difficult to cannulate while the patient is undergoing chest compression.

If technical problems preclude rapid intravenous access, epinephrine, atropine, and lidocaine can be safely instilled into the tracheobronchial tree via an endotracheal tube, in doses equal to initial intravenous doses. Sodium bicarbonate should not be instilled into the lungs.

Except during open-chest massage, the intracardiac injection of medications is indicated only if intravenous or intratracheal administration cannot be done. Potentially serious complications of this route include coronary artery laceration, intramyocardial injection, and pericardial tamponade. Epinephrine is inherently no more effective when administered by the intracardiac route. When intracardiac

administration is indicated, the subxiphoid approach is preferable to the parasternal approach.

Volume expansion with 1 to 2 L of normal saline or another volume expander is often helpful in elevating the blood pressure during resuscitation of the volume-depleted patient, but is not usually useful in the normovolemic patient.

Epinephrine. The most useful and important drug for resuscitation is epinephrine. Although experimental evidence clearly shows that the administration of epinephrine enhances survival in cardiac arrest, this potentially lifesaving drug is often underutilized. Since epinephrine has both α - and β -adrenergic agonist activity in the doses given during resuscitation, it increases both peripheral vasoconstriction (α effect) and cardiac rate and contractility (β effect). This enhancement of peripheral vasoconstriction results in higher rates of successful resuscitation, presumably because of augmented myocardial blood flow resulting from an increase in diastolic blood pressure. Other α agonists, such as methoxamine, phenylephrine, and norepinephrine, may be more effective in this regard, but are less frequently used and less readily available than epinephrine. Methoxamine may actually be superior to epinephrine, since the latter may lead to pulmonary ventilation/perfusion defects during cardiopulmonary resuscitation.

tation. An α -adrenergic agonist should be administered as soon as possible during cardiac resuscitation. Epinephrine in a dose of 1 mg or more intravenously at least every 4 to 5 minutes throughout the duration of the resuscitation, or as a continuous infusion, is the usual choice, but the optimal dose is unknown; doses 10-fold higher than this have dramatically improved survival rates in several animal studies. Frequent administration is necessary due to the rapid metabolism of epinephrine. If intravenous access is unavailable, epinephrine should be given endotracheally by diluting the desired dose in 10 ml of fluid and instilling this into the endotracheal tube. In animals, the success rate of resuscitation is unaffected by β -adrenergic stimulation. For this reason, other β -agonists, such as isoproterenol and dobutamine, usually have no role in the initial phase of cardiac resuscitation. However, these agents may be of value in the patient with bradycardia.

Sodium Bicarbonate. Sodium bicarbonate is frequently used during resuscitation, but its role in resuscitation is extremely controversial. Although valuable for the temporary correction of metabolic acidosis, the premature or excessive use of sodium bicarbonate may result in hypernatremia, the hyperosmolar state, severe arterial alkalemia, or possible excessive CO_2 production peripherally and centrally, thus potentially worsening intracellular and cerebral acidosis. These conditions may be dangerous and may preclude successful resuscitation. Sodium bicarbonate is not proved to beneficially affect the outcome of resuscitation, and must therefore be administered cautiously. In the witnessed arrest, it usually does not need to be given for the first 10 minutes of resuscitation if the patient is being adequately ventilated and metabolic acidosis did not precede the arrest. In the unwitnessed arrest and in the patient with known metabolic acidosis, correction of arterial acidosis may in part be accomplished by hyperventilation-induced hypocarbia. Sodium bicarbonate may still be necessary, usually at an initial dose of 1 mEq/kg. Subsequent doses should be gauged by monitoring the arterial or central venous pH. If blood-gas determinations are unavailable, half of the initial dose of sodium bicarbonate can be administered empirically every 10 to 15 minutes until spontaneous circulation reappears. Sodium bicarbonate inactivates epinephrine and precipitates with calcium chloride, and these drugs should therefore not be administered concurrently through the same intravenous line.

Calcium. Although calcium is necessary for myocardial contraction, few data indicate that calcium salts are therapeutically useful in cardiac resuscitation. Studies have failed to demonstrate a beneficial effect of calcium administration during the attempted resuscitation of patients with asystole or electromechanical dissociation. Moreover, calcium overload may aggravate postischemic injury. Therefore, calcium should be given with caution, if at all, during resuscitation. Appropriate uses for calcium administration include hypocalcemic states, such as after transfusion with large quantities of citrated blood, and hyperkalemia. Calcium administration is contraindicated in patients with digitalis toxicity, owing to the possible aggravation of ventricular dysrhythmias.

Atropine. Atropine, a parasympatholytic drug, is occasionally useful in transiently reversing sinus bradycardia and high-degree atrioventricular block caused by excessive vagal tone. It has little role in the initial stages of resuscitation unless bradycardia is identified as the initial rhythm. The usual dose is 0.5 to 1.0 mg every 5 minutes as needed, to a total of 3 mg. Smaller doses, of 0.2 mg or less, should be avoided because they may cause a paradoxical increase in vagal tone.

Isoproterenol. Isoproterenol is sometimes effective in accelerating the heart rate of patients who remain bradycardic despite atropine, and in patients with complete heart block. The usual dose is 1 to 10 $\mu\text{g}/\text{min}$, titrated down to the smallest dose capable of maintaining an adequate heart rate. Epinephrine has a similar chronotropic efficacy and is often preferable, but neither agent is as effective as artificial pacing.

Antiarrhythmic and Other Drugs. Antiarrhythmic agents can be valuable adjuncts in maintaining sinus rhythm after successful defibrillation. These drugs do not usually directly contribute to restoring sinus rhythm, may raise the threshold for successful cardioversion, and may increase the incidence of post-defibrillation asystole. Therefore, antiarrhythmic agents need not be administered during the initial stage of resuscitation of the patient with ventricular fibrillation. If ventricular tachycardia or ventricular fibrillation is persistent or recurrent, lidocaine (50–75 mg IV every 5 minutes for three doses, followed by a continuous infusion at 1–4 mg/min), or bretylium (5 mg/kg loading dose IV repeated in 10–15 minutes if necessary, to a total dose of 30 mg/kg, followed by a continuous infusion at 1–2 mg/min, if needed) may be useful. These drugs are often used in this sequence. Bretylium may have the unique effect of lowering the defibrillation threshold, but has potentially serious side effects and is not usually recommended as a first-line drug. Isolated reports have also been published of the successful conversion of refractory ventricular fibrillation following the administration of intravenous amiodarone and intravenous magnesium sulfate.

Morphine, β -blockers, corticosteroids, diuretics, nitrates, and calcium-channel antagonists have no proven role in basic cardiac resuscitation.

Mechanical and Electromechanical Support

The emergent use of a transcutaneous external pacemaker or the placement of a pacing wire is often beneficial in the symptomatic bradycardic patient, but is unlikely to resuscitate the asystolic patient. Transvenous pacers are preferable to transthoracic wires, since the latter are less often effective and can be associated with serious complications.

The antishock garment (MAST suit) directs blood flow toward the central circulation and thus may have a role in cardiac resuscitation; its exact place remains to be defined. Mechanical devices to compress the sternum are effective when properly used, and can produce external chest compression more reliably than manual compression. A hand-

held suction device for manual active compression-decompression has also been used on a limited number of patients, and may improve cardiopulmonary circulation over that achieved with standard cardiopulmonary resuscitation.

When Resuscitation is Failing

When resuscitative efforts fail, there is often little that can be done to avert death. However, potentially remediable causes of resuscitative failure do exist. Ventilation may be ineffective, perhaps because of improper endotracheal tube placement or tension pneumothorax. Unreliable intravenous access is often a problem; during frenetic resuscitation efforts, subcutaneous infiltration from an intravenous line may go unnoticed. Severe metabolic abnormalities, such as hyperkalemia, may be present. Volume depletion may be unsuspected and may need empiric treatment if suspicion warrants. Pericardial tamponade may be present; in such instances, pericardiocentesis may result in dramatic hemodynamic improvement. Emergency two-dimensional echocardiography is extremely useful in these differential diagnoses. Resuscitation should not be abandoned until all potentially reversible causes are investigated.

Cerebral Protection and Resuscitation

Despite successful cardiac resuscitation, many patients suffer severe and irreversible ischemic encephalopathy after cardiac arrest. This is due to long periods of cerebral ischemia and to delayed cranial reperfusion after successful restoration of spontaneous circulation. Despite early hopes for effective cerebral protection utilizing high-dose barbiturates, phenytoin, corticosteroids, anticoagulation, hypothermia, and a variety of other measures, there is little evidence that these interventions are beneficial after resuscitation. More recent data indicate that calcium-channel antagonists may have a role in this setting, but further studies are needed before these drugs can be recommended for routine use.

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POTASSIUM HOMEOSTASIS AND HYPERKALEMIC SYNDROMES

Barbara A. Clark, MD and Robert S. Brown, MD

Acute hyperkalemia can be a life-threatening consequence of pathologic, pharmacologic, and iatrogenic disorders. Recognition and prompt therapy often reverses the electrophysiologic complications within minutes. Physicians must therefore have a thorough understanding of potassium homeostasis. These mechanisms keep the serum potassium within the relatively narrow normal range of 4.0 to 5.5 mEq/L despite huge intracellular stores (98% of the total body potassium) and widely varied dietary intake in which the potassium ingested in a day is commonly more than in the entire extracellular fluid. This balance can be upset by changes in renal excretion or by interference with the mechanisms responsible for maintaining the intracellular to extracellular potassium gradient.^{12,66} Frequently a combination of renal and extrarenal abnormalities coexist. For example, although hyperkalemia is prone to occur with any cause of oliguria, this is particularly true when acute renal failure is associated with a large potassium load shifting from the intracellular to extracellular fluid, such as with rhabdomyolysis or a hemolytic transfusion reaction. This discussion, therefore begins with a review of the renal and extrarenal mechanisms that preserve potassium homeostasis.

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RENAL POTASSIUM HOMEOSTASIS

Renal excretion of potassium is modified primarily by the following factors:

- Dietary potassium intake and plasma potassium level
- Distal renal tubular delivery of sodium, poorly reabsorbed anions, and water
- Acid-base balance
- Mineralocorticoids (aldosterone)

Normally renal potassium excretion is highly adaptable to dietary potassium intake in humans.⁵⁶ Although the usual intake of potassium ranges from 1.0 to 1.5 mEq per kg body weight per day, the dietary intake can increase by as much as 6 mEq/kg/day without exceeding the excretory capacity of the kidneys.⁵⁶ The distal tubules and collecting ducts are the sites at which renal potassium excretion is controlled (Fig. 1). Dietary potassium loading stimulates distal tubular $\text{Na}^+-\text{K}^+-\text{ATPase}$ pumps by a direct mechanism independent of mineralocorticoids⁶⁷ in addition to the effects mediated by increasing aldosterone.⁵⁸ This adaptive mechanism enhances renal tubular potassium secretion over about 2 days of a high plasma potassium induced by high dietary intake.⁵⁸

Potassium excretion is also favored by increased delivery of sodium, poorly reabsorbed anions, and water to the distal renal tubular lumen.

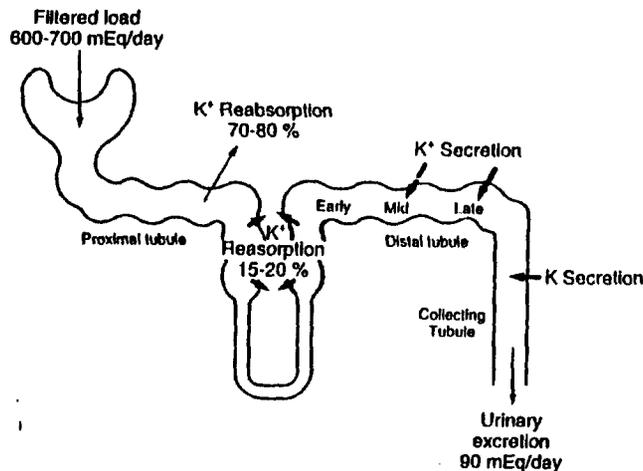


Figure 1. Schematic representation of the renal tubular handling of potassium. Approximately 90% of the filtered potassium is reabsorbed by the early- to mid-distal tubule. Most of the potassium in the urine is derived from secretion of potassium by the mid- to late-distal tubule and cortical collecting tubule. (From Rasteger A, DeFronzo RA: Disorders of potassium metabolism associated with renal disease. In Schrier RW, Gottshalk CW (eds): Diseases of the Kidney, ed 5, vol 3. Boston, Little, Brown & Company, 1993, p 2649; with permission.)

Increased distal tubular delivery of sodium allows enhanced sodium-potassium exchange, with potassium secretion stimulated by the electronegativity of the tubular lumen when sodium is reabsorbed.⁶⁸ The anion accompanying sodium plays a role in this effect because anions other than chloride, such as bicarbonate, phosphate, or sulfate, are relatively impermeant to distal tubular reabsorption. Impermeant anions raise the electronegativity of the tubular fluid when sodium is reabsorbed without an accompanying chloride anion, resulting in increased potassium secretion.⁷⁶ Because overall potassium excretion is dependent on urine flow, increased distal tubular delivery of water also enhances total potassium excretion.⁷⁷ These effects account for the potassium loss seen when renal tubular sodium chloride reabsorption is blocked more proximally by diuretics such as furosemide or thiazides, which act mainly in the loop of Henle or early distal tubule.⁸² Conversely, in states of avid sodium retention, sodium chloride and bicarbonate are more completely reabsorbed in the proximal tubule. The decreased delivery of sodium chloride and bicarbonate to the distal tubule hinders potassium secretion in exchange for sodium. This explains the tendency for hyperkalemia to occur in patients with prerenal azotemia from volume depletion or severe congestive heart failure¹⁶ in which diminished renal perfusion with decreased glomerular filtration rate (GFR) and increased proximal tubular reabsorption of sodium and water result in decreased distal tubular potassium secretion.

Systemic acidosis or alkalosis exerts a powerful effect on renal potassium balance.⁸² In systemic acidosis, hydrogen ion is buffered intracellularly, with a shift of potassium from the intracellular to extracellular fluid to maintain electrical neutrality. When the potassium concentration within the distal tubular cell falls, decreasing the concentration gradient toward the tubular lumen, renal potassium secretion is diminished.¹⁵ Thus the decreased urinary excretion of potassium contributes to hyperkalemia in systemic acidosis. Conversely, with alkalosis, a shift of potassium into distal renal tubular cells promotes enhanced renal tubular potassium secretion. This effect, combined with the increased distal tubular delivery of bicarbonate in patients with metabolic alkalosis, contributes to the increased potassium excretion and hypokalemia.⁷⁰

Aldosterone is the primary mineralocorticoid responsible for potassium homeostasis, acting to increase distal tubular and collecting duct reabsorption of sodium and secretion of potassium (Fig. 2). This effect of aldosterone is mediated by increasing the permeability of the apical membrane sodium channels for sodium and potassium exchange, and secondarily by increasing the number of $\text{Na}^+-\text{K}^+-\text{ATPase}$ pumps.⁶⁹ Adrenal secretion of aldosterone is stimulated directly by an elevated extracellular potassium concentration⁴¹ and by angiotensin II.³⁷ The sensitivity of the adrenal cortex to secrete aldosterone in response to an elevated extracellular potassium level also depends on angiotensin II.³⁷ Thus aldosterone secretion is closely linked to stimulation of the renin-angiotensin system. Renin is secreted in response to salt and water depletion or hypoperfusion of the renal juxtaglomerular apparatus. This

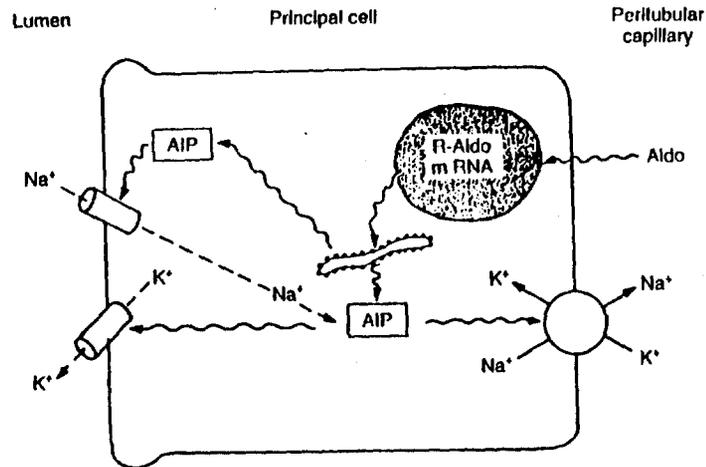


Figure 2. Potassium secretion by the principal cell of the cortical collecting tubule and the effect of aldosterone. Luminal Na^+ enters the cell through Na^+ channels in the apical (luminal) membrane, down a concentration gradient created by the Na-K-ATPase pump (open circle) on the basolateral (peritubular) membrane. The electronegativity of the tubular lumen created by the movement of Na^+ into the cell facilitates the secretion of K^+ through K^+ channels in the luminal membrane. The effect of mineralocorticoids to enhance K^+ secretion is mediated by aldosterone (Aldo) entering the cell and binding to its cytosolic receptor (R-Aldo). The synthesis of aldosterone-induced proteins (AIP) occurs, which increases the number of open Na^+ channels. This allows more Na^+ to be reabsorbed from the luminal fluid into the cell promoting increased K^+ movement into the lumen. The higher intracellular sodium seems to secondarily increase the activity of the Na-K-ATPase pump.⁵⁶ (From Sansom S, Muto S, Gleibisch G: Na-dependent effects of DOCA on cellular transport properties of CCDs from ADX rabbits. *Am J Physiol* 253:F753-F759, 1987; with permission.)

stimulation is mediated in part by beta-sympathetic agonists⁵¹ and by prostaglandins of the E&F series.⁵² As discussed later, interference with this complex renin-angiotensin-aldosterone system can predispose to hyperkalemia.

In summary, renal potassium excretion is enhanced by adaptation to a high-potassium diet; by increased distal tubular delivery of sodium chloride, impermeant anions, and water; by alkalosis; and by increased aldosterone. Conversely, a low-potassium diet, decreased distal tubular delivery of filtrate, acidosis, and decreased aldosterone decrease potassium excretion.

EXTRARENAL POTASSIUM HOMEOSTASIS

Maintenance of normal levels of extracellular potassium depends on renal excretion and on extrarenal disposition of potassium into cells,

mainly muscle cells. This is especially true in patients with renal failure. The major factors known to affect cellular potassium balance are as follows:

- Acid-base balance
- Insulin
- Mineralocorticoids (aldosterone)
- Sympathetic adrenergic activity

Acidosis causes cellular potassium efflux, shifting potassium into the extracellular fluid. In the presence of an excess acid load, there is hydrogen ion influx into the cell in exchange for potassium and decreased cellular potassium uptake by inhibition of $\text{Na}^+\text{-K}^+\text{-ATPase}$.⁵⁹ Together with the decreased renal potassium excretion described in the preceding section, this extracellular shift of potassium can cause hyperkalemia. The opposite occurs in alkalosis, in which a shift of potassium into cells and increased urinary potassium excretion can cause hypokalemia. The effect of acid-base shifts are more substantial in metabolic than respiratory disorders.³ Furthermore, when metabolic acidosis is caused by mineral acids such as hydrochloric acid, the shift of potassium is greater than in organic acidosis, in which there is inhibition of cellular potassium efflux by the accompanying organic anion.³

Basal insulin levels are important in potassium homeostasis because insulin augments cellular potassium uptake.²⁹ Whereas high potassium loads have been shown to stimulate insulin secretion, the magnitude of this effect in humans may be small³⁰ when potassium is given without accompanying dietary glucose intake. Insulin seems to act on potassium uptake by stimulating $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity by a mechanism independent of cyclic AMP and independent of glucose uptake.²⁰ Insulin also stimulates sodium-hydrogen exchange, secondarily augmenting potassium influx by decreasing intracellular hydrogen ion concentration.⁴⁹ The insulin-stimulated cellular uptake of potassium is independent of glucose uptake. This independent action should be remembered when using insulin and glucose to treat hyperkalemia. Glucose should not be given alone, because if insulin secretion is impaired, the increase in serum osmolality caused by the glucose results in an extracellular shift of water and potassium, exacerbating the hyperkalemia.

Although the primary action of mineralocorticoids is to promote renal potassium excretion, aldosterone also plays a role in extrarenal potassium homeostasis. Mineralocorticoids have been shown to increase potassium and decrease sodium content in feces, probably by enhancing colonic epithelial $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity.¹⁷ Aldosterone also increases potassium concentration in saliva and sweat. The amount of potassium excreted via these routes is not usually of physiologic importance unless there is excessive sweating or diarrhea. In addition, fecal potassium secretion seems to be a more important route of excretion in patients with renal failure. Furthermore, aldosterone seems to protect against hyperkalemia resulting from acute potassium loads given to anephric patients,⁷² presumably by augmenting cellular potassium uptake in tissues with mineralocorticoid receptors.

Sympathetic adrenergic activity also plays an important role in potassium distribution. Beta-adrenergic stimulation increases and beta-blockade impairs extrarenal disposal of a potassium load.⁶¹ This occurs independently of any change in insulin or aldosterone levels and without affecting renal potassium excretion.⁶¹ The increased cellular potassium uptake seems to be a beta₂-specific effect because it is stimulated only by beta₂ agonists and blocked only by beta₂ antagonists.¹¹ The cellular mechanism depends on binding to beta receptors and stimulation of cyclic AMP via adenylate cyclase, which in turn activates the Na⁺-K⁺-ATPase pump, resulting in sodium efflux and potassium influx across the cell membrane.¹⁹ In contrast, alpha-adrenergic stimulation seems to inhibit cellular potassium uptake.⁶¹ For example, in exercise-induced hyperkalemia, beta blockade with propranolol augments and alpha blockade with phentolamine diminishes the rise of extracellular potassium.⁷⁰ In summary, alkalosis, increased insulin, increased aldosterone, and beta-adrenergic stimulation enhances extrarenal uptake of a potassium load. Conversely, acidosis, decreased insulin, decreased aldosterone, and alpha-adrenergic stimulation or beta blockade enhances cellular potassium efflux, causing hyperkalemia.

ETIOLOGY OF HYPERKALEMIA

Multiple mechanisms control potassium balance and act to prevent hyperkalemia. Frequently, however, one or more partial defects in these homeostatic mechanisms exist. The patient population particularly at risk for hyperkalemia are diabetics in whom insulin deficiency, autonomic insufficiency (with decreased beta-adrenergic stimulation), propensity for acidosis, renal insufficiency, and hyporeninemic hypoaldosteronism may coexist.⁶² Physicians must be aware of disease states and drugs that predispose to hyperkalemia to prevent potentially dangerous pharmacologic regimens. Four general causes of hyperkalemia should be remembered when evaluating a specific patient: (1) diminished potassium excretion; (2) intracellular to extracellular potassium shift; (3) excess potassium load; and (4) pseudohyperkalemia. The following list elaborates on these four basic causes:

- Diminished renal potassium excretion
 - Oliguric renal failure
 - Severe nonoliguric renal failure (GFR usually < 10 mL/min)
 - Distal tubular renal diseases with defective potassium secretion
 - Acute interstitial nephritis, often drug induced
 - Sickle cell nephropathy
 - Renal transplant rejection
 - Reflux and obstructive uropathies
 - Papillary necrosis
 - Lead nephropathy
 - Lupus interstitial nephritis
 - Pseudohypoaldosteronism

- Mineralocorticoid deficiency with decreased renal tubular potassium secretion
 - Addison's disease
 - Hypoaldosteronism with or without low renin levels
- Drugs that inhibit potassium secretion
 - Decreased aldosterone secretion
 - Heparin
 - Angiotensin-converting enzyme inhibitors
 - Decreased distal tubular potassium secretion
 - Potassium sparing diuretics: spironolactone, amiloride, triamterene
 - Trimethoprim
 - Lithium toxicity
 - Decreased aldosterone and decreased renal tubular potassium secretion
 - Nonsteroidal antiinflammatory drugs
 - Cyclosporine and tacrolimus
- Intracellular to extracellular shifts of potassium
 - Acidosis, particularly metabolic mineral acidosis
 - Hyperosmolar syndromes
 - Insulin deficiency
 - Autonomic nervous system insufficiency
 - Vigorous exercise
 - Cell necrosis
 - Rhabdomyolysis
 - Acute hemolysis
 - Drugs that shift potassium extracellularly
 - Beta-adrenergic blockers
 - Alpha-adrenergic agonists
 - Digitalis intoxication
 - Fluoride poisoning
 - Tumor cell lysis
 - Depolarizing muscle relaxants
 - Arginine hydrochloride
 - Hyperkalemic periodic paralysis
 - Excess exogenous potassium loads
 - High oral or intravenous potassium intake
 - Potassium-containing salt substitutes
 - Potassium penicillin G
 - Pseudohyperkalemia
 - Hemolyzed blood sample
 - Thrombocytosis, usually over 800,000/mm³
 - Marked leukocytosis, usually over 100,000/mm³

DIMINISHED POTASSIUM EXCRETION

Although the most obvious cause of diminished potassium excretion is renal failure, many other systemic conditions and pharmacologic agents significantly influence renal potassium metabolism. Acute hyper-

kalemia is most commonly seen associated with oliguria (either renal or prerenal) in which a marked decrease in potassium excretion occurs. In nonoliguric acute or chronic renal failure, the GFR usually is less than 10 mL/min before hyperkalemia occurs. There are certain renal diseases, however, in which selective tubular dysfunction occurs before a significant decrease in GFR. Decreased renal tubular potassium secretion creates a disproportionate susceptibility to hyperkalemia. Distal tubular diseases include drug-induced allergic interstitial nephritis,²² sickle cell nephropathy,⁶ renal transplant rejection,²⁸ reflux and obstructive nephropathies,³ lead nephropathy,³¹ papillary necrosis, and some cases of lupus nephritis.²⁷

As described under the section on renal potassium homeostasis, acidosis diminishes renal potassium secretion. Acute renal failure may be accompanied by acidosis secondary to accumulation of organic acids or concomitant lactic acidosis or ketoacidosis, which exacerbates hyperkalemia. Correcting the acidosis in acute or chronic renal failure usually helps to control the hyperkalemia.

Pseudohypoaldosteronism is a rare disorder in which aldosterone levels are normal but urinary potassium secretion is low.^{4, 65} Hyperkalemia occurs secondary to an apparent defect in renal aldosterone receptors in one type of infantile pseudohypoaldosteronism.⁴ In infants an associated salt wasting and hypotension occur,⁴ whereas in adults, hypertension and acidosis occur.⁶⁵ Mineralocorticoids are ineffective as treatment. Increasing renal potassium excretion by a thiazide diuretic or sodium sulfate often is useful in controlling the hyperkalemia in these patients.⁶⁵

Primary adrenal insufficiency (Addison's disease) is a well-recognized, although infrequent, cause of hyperkalemia. Diagnosis is confirmed by low plasma cortisol and aldosterone levels with a blunted response to corticotropin (Cortrosyn stimulation test).

Hyporeninemic hypoaldosteronism is increasingly recognized as a cause of hyperkalemia.⁶⁴ It is characterized by an associated hyperchloremic acidosis and low levels of renin and aldosterone.⁶⁴ In some patients, renin levels may be normal but with suppressed secretion of aldosterone dependent on another mechanism. Volume-overload states with increased levels of atrial natriuretic peptide may play a role⁷⁸ because atrial natriuretic peptide has been shown to suppress aldosterone stimulation induced by potassium loading.¹⁸ The typical patient is elderly, often having diabetes and mild renal insufficiency. Because the aldosterone defect is only partial, salt wasting and hyponatremia usually are not seen. Mineralocorticoid replacement (0.1 mg and occasionally up to 0.4 mg daily of fludrocortisone) is effective treatment but may provoke fluid retention and hypertension, requiring thiazide or loop diuretic therapy. Correction of the acidosis with oral sodium bicarbonate, however, may be sufficient to correct the hyperkalemia in some patients.

A variety of drugs can interface with the renin-angiotensin-aldosterone axis and thereby promote hyperkalemia. Heparin suppresses adrenal cortical aldosterone synthesis by inhibiting conversion of corticosterone to 18-hydroxycorticosterone.⁵¹ In most circumstances this is not

significant enough to produce hyperkalemia. When a patient has an already compromised renin-angiotensin-aldosterone system, however, the heparin effect may cause elevated serum potassium levels.³¹

Angiotensin-converting enzyme inhibitors such as captopril or enalapril have been increasingly prescribed in treating hypertension and congestive heart failure. They prevent the conversion of angiotensin I to angiotensin II and thereby reduce aldosterone secretion.⁷⁴ Hyperkalemia is most likely to occur in patients with renal insufficiency⁷⁴ or those with severe congestive heart failure in whom renal perfusion and, therefore, distal tubular sodium delivery is low.⁴⁶

Several diuretics are prescribed for their potassium-sparing properties. Spironolactone is an aldosterone antagonist.²⁵ The actions of triamterene and amiloride are independent of aldosterone. Amiloride inhibits distal tubular cell sodium channel permeability, thereby interfering with sodium reabsorption, which is the driving force for potassium secretion.⁷ Triamterene seems to inhibit the sodium channel and may inhibit Na⁺-K⁺-ATPase activity at the basolateral cell membrane.⁴² Any of the potassium-sparing diuretics may cause significant hyperkalemia by decreasing renal potassium excretion. A recently recognized cause of hyperkalemia is high-dose trimethoprim when treating pneumonia from a *Pneumocystis carinii* infection in immunologically deficient patients.⁷⁵ The mechanism is apparently an effect of trimethoprim to block the sodium channel similar to amiloride.⁷⁵

Nonsteroidal antiinflammatory drugs (NSAIDs) also may predispose to hyperkalemia. Renal prostaglandins are necessary for adequate renin production by the juxtaglomerular apparatus. By inhibiting prostaglandin synthesis, NSAIDs produce iatrogenic hyporeninemic hypoaldosteronism.⁷³ In addition, prostaglandins decrease sodium chloride reabsorption in the loop of Henle, thereby augmenting the distal tubular delivery of sodium and the sodium-potassium exchange. Again, patients at risk for hyperkalemia from NSAIDs include those who have renal failure, diabetes, or those who are taking other agents that interfere with potassium homeostasis.⁷⁶

Cyclosporine and tacrolimus—immunosuppressant drugs used frequently in transplant recipients—have been associated with hyperkalemia even in patients with normal GFR and without evidence of renal transplant rejection. An associated hyperchloremic metabolic acidosis frequently occurs. Although the mechanism remains unclear, cyclosporine seems to produce both hypoaldosteronism and tubular nephrotoxicity with decreased renal tubular potassium secretion.^{33, 55} Lithium toxicity is a rare cause of hyperkalemia²³; it apparently acts by decreasing renal tubular potassium excretion.³⁴

INTRACELLULAR TO EXTRACELLULAR POTASSIUM SHIFTS

Acidosis is probably the most common reason for an acute shift of potassium to the extracellular fluid and can cause severe hyperkalemia.

An acute mineral acidosis often is accompanied by a serum potassium rise of 0.5 to 1.3 mEq/L for every 0.1-unit fall of arterial pH; organic and respiratory acidoses usually provoke lesser rises in the serum potassium unless they are accompanied by cell necrosis or insulin deficiency.

When plasma tonicity is acutely raised, as in hyperglycemia⁵⁰ or infusion of mannitol,⁵⁰ plasma potassium also rises. With the rise in osmolality, fluid shifts from the intracellular to the extracellular space and potassium accompanies this water flux. In normal persons, hyperglycemia induces insulin release, which augments cellular potassium uptake. Therefore glucose-induced hyperkalemia usually is clinically significant only in the insulin-deficient person with type I diabetes mellitus.⁵¹

In insulin deficient persons, decreased tolerance to a potassium load may cause hyperkalemia.⁹ Because insulin is an important mediator of cellular potassium uptake, the diabetic must rely on other mechanisms to maintain potassium homeostasis. If these are impaired also, serious hyperkalemia may result.

Beta-adrenergic blockade and alpha-adrenergic stimulation impair the extrarenal disposal of potassium loads. Beta-blocking agents produce only a small increment in plasma potassium in normal persons⁸ but should be used with caution in patients with renal failure.⁵¹ Although less commonly used, alpha-adrenergic agonists, such as phenylephrine, can contribute to hyperkalemia.⁵¹

Digitalis intoxication can produce severe hyperkalemia.⁶⁴ The mechanism is believed to be from poisoning of the Na⁺-K⁺-ATPase pump throughout all body tissues. Extracellular potassium rises while intracellular potassium falls. This results in reduction of the resting membrane potential, decreased automaticity, and resultant cardiac arrhythmias. Therapeutic digoxin levels are not high enough to affect potassium levels. In severe cases of hyperkalemia caused by digitalis intoxication, digoxin immune Fab fragment (Digibind) can be life-saving.⁶⁴ In patients with renal failure receiving hemodialysis, accidental fluoride poisoning may cause fatal hyperkalemia by an intracellular to extracellular shift of potassium.⁶⁷

Vigorous exercise may cause an acute elevation in serum potassium. This is partly caused by a potassium release from contracting muscle cells. Ordinarily this presents no physiologic problem. An exaggerated plasma potassium rise, however, can occur in patients taking beta blockers or alpha agonists.⁷⁹

Massive cellular necrosis can lead to an acute release of potassium into the extracellular fluid that can overwhelm the potassium disposal mechanisms, particularly if renal failure is present. Rhabdomyolysis, traumatic muscle injury (crush syndrome), or hemolytic transfusion reactions can produce simultaneous renal failure and life-threatening hyperkalemia. Early institution of dialysis often is necessary to control the hyperkalemia in these patients. Acute hyperkalemia may be caused by chemotherapy²⁴ when necrosis of a large tumor burden releases intracellular potassium into the extracellular fluid. This is seen mostly

in the treatment of leukemia or lymphoma. Often an associated release of uric acid occurs, with acute urate nephropathy or renal toxicity from certain chemotherapy agents that also compromises renal potassium excretion.

Plasma potassium rises slightly (about 0.5 mEq/L) in patients given depolarizing muscle relaxants, such as succinylcholine, because of efflux of potassium from motor end plates.⁴⁰ In certain disease states, life-threatening hyperkalemia can occur. Patients at risk include those with massive trauma, burns, tetanus, and neuromuscular or central nervous system diseases.⁴³ The mechanism for this remains unclear but may be caused in part by exaggerated potassium release from either sensitized or proliferating motor end plates.

Intravenous arginine hydrochloride occasionally is used in treating severe metabolic alkalosis. In normal subjects a standard 30- to 60-g dose is associated with a 0.6- to 1.0-mEq/L rise in serum potassium. Arginine hydrochloride is a cationic amino acid that displaces intracellular potassium to the extracellular space. Severe hyperkalemia has been reported in patients with renal failure and in patients with hepatic insufficiency who are unable to metabolize the arginine.¹⁴

Hyperkalemic periodic paralysis is a rare inherited disorder of potassium homeostasis characterized by sudden onset of paralysis and hyperkalemia precipitated by anesthesia, fasting, strenuous exercise, or potassium ingestion.⁷¹ The pathogenesis remains unclear. Aldosterone, insulin, and the adrenergic system are intact.^{21, 45} A generalized disorder of potassium transport seems to occur. Besides avoiding known precipitants, treatment with diuretics or the beta agonist, salbutamol, have been of therapeutic benefit.⁷⁷

Excess Exogenous Potassium Load

Elevations in serum potassium can occur after massive administration of oral potassium (> 2.5 mEq/kg) or intravenous infusion of greater than 40 mEq/h.¹² The use of potassium-containing salt substitutes can supply as much as 1.2 to 5.7 mEq of potassium per "shake." These salt substitutes pose a danger to patients with renal failure, diabetes, infants, those taking potassium-sparing diuretics, and, rarely, normal elderly persons who use them too heavily. Some high-protein, high-calorie nutrient supplements contain substantial amounts of potassium, and if given in large quantities to debilitated patients with low muscle mass, can result in acute hyperkalemia.

Potassium supplements frequently are prescribed for patients taking thiazide or loop diuretics. Hyperkalemia is unlikely to occur in normal persons unless a significant overdose is taken but is more common in patients with renal insufficiency. Rapid administration of penicillin G can account for a substantial potassium load. It contains 1.7 mEq potassium per million units of penicillin, and large doses should not be given by intravenous bolus. The sodium preparation of penicillin G is safer in patients with renal failure.

Pseudohyperkalemia

Spurious hyperkalemia can occur secondary to release of potassium from intracellular stores after a blood sample is collected. For example, a traumatic venipuncture, prolonged tourniquet use, or excessive blood sample agitation can hemolyze red cells and release potassium. Potassium release from platelets or white blood cells during *in vitro* coagulation can produce a 1.0- to 1.5-mEq/L elevation in serum potassium in patients with thrombocytosis (usually over 800,000/mm³) or extreme leukocytosis (> 100,000/mm³).

EVALUATION OF HYPERKALEMIA

Although the development of hyperkalemia often is multifactorial, the detection of the major causes usually is possible. Knowledge of potassium homeostatic mechanisms and possible causes of hyperkalemia point the clinician toward the evaluation necessary. When pseudohyperkalemia is suspected, collection of blood in a heparinized tube should reflect the true plasma potassium to be normal in these cases.

Persistent hyperkalemia commonly results primarily from either renal failure or an inadequate renal tubular secretion of potassium. Measurement of urinary excretion of potassium in hyperkalemic patients without renal failure usually differentiates between disorders of renal and extrarenal potassium homeostasis.^{32,34} If renal excretion is inappropriately low, the administration of a mineralocorticoid can differentiate between hormonal and renal tubular defects. The transtubular potassium gradient (TTKG), calculated from a random urine specimen using the following formula, estimates the tubular fluid potassium concentration at the site of most potassium secretion, the end of the cortical collecting tubule:

$$\begin{aligned} \text{TTKG} &= \frac{\text{Urine K}}{\text{Plasma K} \cdot \frac{\text{Uosm}}{\text{Posm}}} \\ &= \frac{\text{Urine K} \cdot \text{Posm}}{\text{Plasma K} \cdot \text{Uosm}} \end{aligned}$$

where K is potassium, Posm is plasma osmolality, and Uosm is urine osmolality.

The TTKG corrects for the increase of urinary potassium concentration effected by water extraction in the medullary collecting duct without any increment of potassium secretion. Because increased renal excretion of potassium with potassium loading in normal subjects increases the TTKG from baseline levels of about 8 to over 10², values over 8 indicate a normal renal response to hyperkalemia and argue for an extrarenal cause (i.e., a high exogenous or endogenous potassium load). Con-

versely, TTKG values below 6 are indicative of a renal excretory defect.³⁴ In cases with a low TTKG, the administration of a mineralocorticoid (either 100 mg of hydrocortisone or 0.1 mg of fludrocortisone acetate) should increase the TTKG to over 6 after 4 hours in patients with mineralocorticoid deficiency. Combined with the documentation of a low plasma aldosterone, a low but responsive TTKG confirms hypoaldosteronism, whereas an unresponsive TTKG points to a tubular secretory defect of a renal cause.³⁴ The latter might be caused by either a primary renal tubular disease or a potassium-sparing diuretic. The TTKG formula approach, however, may not be useful in subjects with low distal delivery of sodium (< 25 mEq/L) compromising maximal potassium secretion, or with a water diuresis causing a low urinary potassium concentration,³² even if normal renal tubular secretory mechanisms are intact.

Once the clinician distinguishes that the disorder is of either a hormonal, renal tubular, or extrarenal cause, it is usually possible to detect the major factors responsible.

MANIFESTATIONS OF HYPERKALEMIA

Although exceptions exist, clinical symptoms are rare unless the hyperkalemia is severe. Hyperkalemic manifestations are primarily muscular and cardiac.³⁰ Patients may complain of generalized muscle weakness or dyspnea secondary to respiratory muscle weakness. Rapid development of hyperkalemia can produce paradoxical tetany-like symptoms of muscle twitching and tingling.³² If hyperkalemia is severe, flaccid paralysis may be present. Frequently, however, no outward clinical symptoms occur and patients develop cardiac dysrhythmias as the initial manifestation. Early electrocardiographic changes include peaking of T waves and shortening of the QT_c interval, followed by loss of P waves, widening of the QRS complex, and eventually a sine wave pattern in which the widened QRS merges with an adjacent T wave. Electrocardiogram (ECG) changes seldom are seen with a serum potassium level less than 6.0 mEq/L and frequently are present with a potassium level of more than 8.0 mEq/L.³⁰

TREATMENT OF HYPERKALEMIA

Effective therapy takes advantage of mechanisms to enhance intracellular potassium uptake and maximize potassium elimination via renal and extrarenal routes. The primary approaches to treating hyperkalemia are as follows:

- Antagonize potassium cardiac toxicity
 - Calcium chloride or gluconate intravenously
- Shift potassium into cells
 - Sodium bicarbonate intravenously

- Insulin intravenously with glucose to avoid hypoglycemia
- Albuterol by inhalation or intravenously
- Enhance potassium excretion
 - Furosemide diuresis
 - Sodium polystyrene sulfonate orally or by rectal enema
 - Dialysis: hemodialysis or peritoneal dialysis
- Avoid excessive potassium intake

Electrocardiographic monitoring should be started and continued throughout the treatment course. If no ECG changes are present, hemolysis or thrombocytosis should be ruled out quickly as possible causes of pseudohyperkalemia.

Mild hyperkalemia without ECG changes can be treated by enhancing potassium clearance from the body. Administering a cation exchange resin, sodium polystyrene sulfonate (Kayexalate, 15 to 20 g in 50 to 80 mL of water, with or without 10 mL of a 70% sorbitol solution to prevent constipation) given orally every 2 hours (up to five doses) facilitates potassium loss from the gastrointestinal tract. Although the resin can be administered rectally (50 g in 100 mL of 10% sorbitol or dextrose solution by enema every 4 to 6 hours), it is more effective if taken orally because of increased retention time. Each 1 g of the resin given orally removes about 1 mEq of potassium. The use of sodium polystyrene sulfonate with sorbitol should be avoided in postoperative patients, particularly those who are immune suppressed with renal transplants, because bowel perforation has been described in this setting.⁵⁸ Additionally, furosemide administration can be used to enhance renal potassium excretion if a diuresis ensues. When hyperkalemia is accompanied by or is secondary to metabolic acidosis, administration of sodium bicarbonate may be sufficient to correct both abnormalities.

If the serum potassium elevation is severe (> 7.0 mEq/L) or is moderate (6.0–7.0 mEq/L) and associated with ECG changes, more urgent therapy is indicated. Initial treatment is directed toward effecting an acute increase in cellular potassium uptake, thereby reducing extracellular potassium concentration. Administration of two to three ampules of sodium bicarbonate (50 mEq per ampule) intravenously usually produces a shift of potassium intracellularly over 20 minutes. Several studies, however, have failed to confirm a reliable effect of sodium bicarbonate to lower the serum potassium in patients with end-stage renal disease.⁶² Insulin administration therefore may be a more logical first therapy in such cases, with sodium bicarbonate added in cases of acidosis. If concomitant hypocalcemia is present (as may occur with acute or chronic renal failure), care should be taken to precede alkalization with the administration of calcium salts because the acidosis may be protecting against tetany.

Insulin administration also produces an increase in cellular potassium uptake over 20 to 30 minutes, and the decrease of the serum potassium is greater than with sodium bicarbonate.¹⁰ The usual dose is

10 units of regular insulin by intravenous bolus accompanied by one ampule of 50 mL of 50% dextrose to prevent hypoglycemia, but several alternative regimens have been used.⁶²

Albuterol, by nebulized inhalation of 10 mg² or intravenous infusions of 0.5 mg,^{44, 46} also has been shown to be a rapid way to reduce the serum potassium by its beta-agonist action to promote cellular uptake. In addition, in some studies combining albuterol with insulin resulted in a greater decrease in the plasma potassium than giving either drug alone.^{1, 44} The safety of this treatment to avoid cardiac tachyarrhythmia and angina, however, has not been documented, suggesting that albuterol should be reserved for situations in which the foregoing treatments are ineffective or undesirable.⁶²

If ECG changes are severe (widened QRS complex), intravenous calcium also should be given. Calcium has an immediate protective effect by raising myocardial cell membrane threshold potential and restoring excitability toward normal. Calcium can be administered as either two to four 10-mL ampules of 10% calcium gluconate or one 10-mL ampule of 10% calcium chloride intravenously over 2 to 5 minutes. Because calcium gluconate releases ionic calcium more slowly into the circulation, it is safer and will not cause skin necrosis if extravasated. Calcium chloride, however, may be more effective if the patient is in cardiac arrest with poor tissue perfusion. If concomitant digitalis intoxication is suspected, calcium should not be administered unless the serum calcium is low to avoid precipitation of ventricular fibrillation.

In addition to the acute therapy with sodium bicarbonate, insulin, and calcium salts, some means of ridding the body of excess potassium must be initiated. Sodium polystyrene sulfonate resin usually is effective but may be inadequate if there is compromise of the gastrointestinal tract, large potassium loads, or inability to tolerate the sodium released from the resin (about 1–1.3 mEq/g). In such cases, dialysis is an effective method of potassium removal. Hemodialysis is more efficient than peritoneal dialysis for this purpose.

Equally important to prevent recurrent hyperkalemia, the clinician must search for the underlying disturbances and eliminate any reversible factors that predispose to hyperkalemia.

In summary, potassium excretion is dependent on the physiologic influences that control renal distal tubular and cortical collecting duct secretion of potassium and thereby determine the total body potassium content. The factors affecting renal potassium excretion and the disorders that lead to potassium retention and hyperkalemia are reviewed. In addition, extrarenal mechanisms promote cellular uptake of potassium to preserve the normal distribution of potassium between the intracellular and extracellular fluid compartments. Knowledge of the pathophysiologic features of these renal and extrarenal mechanisms usually allows the proper distinction and treatment of clinical disorders of potassium homeostasis.

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