

# REVIEWS OF THERAPEUTICS

## Pharmacotherapy Considerations in Advanced Cardiac Life Support

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Cardiac arrest and sudden cardiac death remain major causes of mortality. Early intervention has been facilitated by emergency medical response systems and the development of training programs in basic life support and advanced cardiac life support (ACLS). Despite the implementation of these programs, the likelihood of a meaningful outcome in many life-threatening situations remains poor. Pharmacotherapy plays a role in the management of patients with cardiac arrest, with new guidelines for ACLS available in 2005 providing recommendations for the role of specific drug therapies. Epinephrine continues as a recommended means to facilitate defibrillation in patients with pulseless ventricular tachycardia or ventricular fibrillation; vasopressin is an alternative. Amiodarone is the primary antiarrhythmic drug that has been shown to be effective for facilitation of defibrillation in patients with pulseless ventricular tachycardia or fibrillation and is also used for the management of atrial fibrillation and hemodynamically stable ventricular tachycardia. Epinephrine and atropine are the primary agents used for the management of asystole and pulseless electrical activity. Treatment of electrolyte abnormalities, severe hypotension, pulmonary embolism, acute ischemic stroke, and toxicologic emergencies are important components of ACLS management. Selection of the appropriate drug, dose, and timing and route of administration are among the many challenges faced in this setting. Pharmacists who are properly educated and trained regarding the use of pharmacotherapy for patients requiring ACLS can help maximize the likelihood of positive patient outcomes.

**Key Words:** advanced cardiac life support, ACLS, cardiac arrest, pharmacotherapy, pharmacist's role, antiarrhythmic drugs, epinephrine, vasopressin.  
(*Pharmacotherapy* 2006;26(12):1703–1729)

### OUTLINE

Role of Drug Therapy  
Pulseless Ventricular Tachycardia or Fibrillation  
    Vasoactive Agents  
    Antiarrhythmic Agents  
Tachyarrhythmias  
    Paroxysmal Supraventricular Tachycardia  
    Atrial Fibrillation or Flutter  
    Wide-Complex Tachycardias  
    Torsade de Pointes  
Asystole, Pulseless Electrical Activity, Symptomatic  
Bradycardia

Atropine  
Hyperkalemia and Hypokalemia  
    Sodium Bicarbonate  
    Calcium  
Hypotension  
Pulmonary Embolism  
    Thrombolytic Therapy  
Acute Ischemic Stroke  
    Thrombolytic Therapy  
Toxicology: Agents for Reversal  
    Glucagon  
    Calcium

Catecholamines  
Digoxin Immune Antibody Fragments  
Therapeutic Hypothermia  
Key Elements in Drug Administration  
Role of the Pharmacist  
Conclusion

Early interventions for successful resuscitation, such as mouth-to-mouth breathing and application of electricity to terminate ventricular fibrillation arrest, were described in the late 1950s.<sup>1,2</sup> Chest compressions to sustain life were first performed in the 1960s, which led to the concept of combined chest compressions and mouth-to-mouth respiration,<sup>3</sup> which is known today as cardiopulmonary resuscitation (CPR). In 1966, the National Academy of Sciences' National Research Council held the first conference on CPR.<sup>4</sup> Subsequently, the American Heart Association and American Academy of Pediatrics developed guidelines by using an algorithmic approach to the management of patients with various types of medical emergencies. The guidelines and standards were revised in 1973, 1979, 1985, 1992, 2000, and, most recently, in 2005.<sup>5</sup> In 2000, the first international guidelines conference was held to produce evidence-based global resuscitation guidelines in which interventions were graded on the basis of available supporting literature.<sup>3,5-8</sup> A new set of American Heart Association-International Liaison Committee on Resuscitation (ILCOR) guidelines were released in November 2005<sup>5,8</sup>; the classification system and its definitions are listed in Table 1.

Four key elements, known as the links in the chain of survival, are associated with an increased likelihood of survival in patients with sudden cardiac arrest: early access, early CPR, early defibrillation, and early advanced cardiac life support (ACLS).<sup>9</sup> Additional factors that may influence survival include the setting of the event

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(witnessed, community, or in-hospital), initial cardiac rhythm, and preexisting medical conditions.<sup>10,11</sup> To improve the delivery of prompt basic life support, general public training programs and emergency medical response systems were developed to facilitate reducing the time to initiation of CPR, respiratory support including intubation, defibrillation, and administration of drugs. More recently, automatic external defibrillators have been developed and are available in airplanes, shopping malls, airports, and residential areas, and even for purchase for home use, to further reduce the time to treatment while awaiting emergency medical response.<sup>12</sup> First responders in the public trained in both CPR and the use of automatic external defibrillators when available to deliver early defibrillation have been shown to improve survival to hospital discharge.<sup>13</sup>

A more rapid transition from basic life support to ACLS may take place during cardiac arrests that occur at a hospital or clinic, where trained medical personnel have rapid access to defibrillators, other necessary equipment, and drug therapy. A 3-4-fold delay in the time of initial administration of drug therapy and prolonged intervals between drug doses have been reported when ACLS is delivered in the field compared with the in-hospital setting; this delay may impact survival.<sup>14</sup> For every 1-minute delay in recognition and defibrillation, there is a resultant 10% reduction in the chance of a successful intervention.<sup>14-16</sup> Only one in every three patients who experience an out-of-hospital cardiac arrest survives to hospital arrival, and only 3-13% survive to discharge.<sup>17,18</sup> More rapid defibrillation of rhythms such as pulseless ventricular tachycardia or fibrillation in hospitalized patients increases the chances of survival.<sup>19</sup> Systems that rapidly and proactively identify and treat patients in acute care settings at risk for clinical deterioration, potentially leading to respiratory or cardiac arrest, can improve outcomes.<sup>20</sup> In spite of this, long-term prognosis of hospitalized patients requiring CPR may actually be poorer, due to greater clinical acuity, a higher likelihood of cardiac disease, advanced age, and concurrent influencing drug therapies. The most common initial rhythms occurring in hospitalized patients experiencing cardiac arrest are asystole and pulseless electrical activity (PEA), which are associated with low survival rates.<sup>21,22</sup> In the Antiarrhythmics versus Implantable Defibrillators (AVID) trial, mortality associated with sustained life-threatening ventricular arrhythmias was

**Table 1. Classification of Recommendations for Interventions in Advanced Cardiac Life Support<sup>3,5</sup>**

| Class         | Definition  |
|---------------|---|
| I             | Data are obtained from large, randomized clinical trials or meta-analyses. Benefit of therapy far exceeds the risk. Intervention is always acceptable, proven safe, and useful.   |
| IIa           | Data are obtained from randomized controlled trials, but trial size is small and less significant effect of treatment. Benefit of therapy exceeds the risk. Intervention is considered standard of care and is acceptable, safe, and useful.    |
| IIb           | Data are obtained from small, nonrandomized, prospective cohort studies with variable outcomes. Based on more expert opinion. Benefit is equal to risk of a given treatment. Intervention may be considered (i.e., optional or an alternative). |
| III           | No data supporting positive clinical outcomes exist. Data may suggest harm. No benefit derived from the treatment and may be harmful. Intervention should not be performed.   |
| Indeterminate | New research or continuing area of investigation. No recommendation on the use of the intervention until more data are available.   |

significantly higher in hospitalized patients compared with that in individuals who developed out-of-hospital cardiac arrest at 1 year (23% vs 10.5%) and 2 years (31% vs 16.5%).<sup>23</sup>

In patients with pulseless ventricular fibrillation or tachycardia, only rapid, competent basic life support and prompt defibrillation have been shown to unequivocally improve survival by reestablishing cardiac output, electrical conduction capable of sustaining blood flow, and oxygen delivery to vital organ systems (brain and heart) and by return of spontaneous circulation (ROSC).<sup>24</sup> There is diminishing value if ROSC is not established after the first defibrillation shock.<sup>17</sup> Ultimately, successful outcomes are based on attaining self-sustaining circulation, cardiac rhythm, and cerebral function.

### Role of Drug Therapy

Administering adjunctive pharmacotherapy must be coordinated with the administration of each nonpharmacologic treatment modality. For instance, in patients with pulseless ventricular tachycardia resistant to initial defibrillation, adjunctive drug therapy may be considered to enhance the likelihood of ROSC. However, if the next defibrillation shock is applied immediately after administration of a drug, as recommended in the 2005 guidelines, there may be insufficient time for the agent to circulate to the heart to reach target receptors and facilitate defibrillation.<sup>8</sup> Therefore, after the administration of each drug, CPR should be continued to facilitate drug distribution to the heart in order to optimize a response. In addition, the administration of a 10–20-ml bolus of normal saline after each drug can assist drug distribution.<sup>8</sup> Available intravenous access sites such as a peripheral antecubital

or external jugular vein require a longer path for drug distribution than does a central intravenous access site such as the internal jugular vein. Drugs used for specific ACLS indications, recommended doses, and classes of recommendation are presented in Table 2.

### Pulseless Ventricular Tachycardia or Fibrillation

#### Vasoactive Agents

In the absence of adequate circulation, vasoconstricting drugs such as catecholamines or vasopressin may enhance organ perfusion by increasing arterial and aortic diastolic pressures, resulting in desirable increases in cerebral and coronary perfusion pressures, while reducing blood flow to visceral and muscle tissues.<sup>25</sup> Increased coronary perfusion pressure and myocardial blood flow are associated with increased success of defibrillation and ROSC.<sup>26, 27</sup>

Available catecholamine agents exert effects on different receptors. Adrenergic  $\alpha_1$ -receptors may be desensitized during cardiac arrest, whereas adrenergic  $\alpha_2$ -agonist activity may be beneficial. Stimulation of adrenergic  $\beta$ -receptors may increase myocardial oxygen consumption with potentially deleterious effects.<sup>28</sup> Catecholamine agents such as epinephrine act primarily by the stimulation of endogenous  $\alpha$ - and  $\beta$ -receptors. Limited evidence suggests that epinephrine, depending on the rhythm and situation, may or may not improve the chance of initial ROSC.<sup>26, 29–31</sup>

#### Epinephrine

Although no randomized trials have compared the efficacy of epinephrine with that of placebo, epinephrine is currently the preferred initial catecholamine recommended in ACLS for

Table 2. The 2005 Advanced Cardiac Life Support Classification of Drugs for Specific Indications<sup>5</sup>

| Drug         | Rhythm Indication                                     | Dose                                   | Class Recommendation | Comments   |
|--------------|---|--|----------------------|--|
| Adenosine    | SVT   | 6 mg                                   | I                    | Must be administered rapidly. May be repeated at dose of 12 mg for 2 additional doses. In patients taking carbamazepine or dipyridamole, or in cardiac transplant recipients, use initial dose of 3 mg.  |
| Amiodarone   | Pulseless VT or VF                                    | 300-mg i.v. bolus                      | IIb                  | No dilution required. May repeat with 150 mg i.v. in 3–5 min.  |
|              | Stable VT   | 150 mg                                 | IIb                  | To avoid hypotension, administer over 10 min. Dose may be repeated as needed to a maximum of 2.2 g/24 hrs. One option is to follow the bolus with a continuous infusion at 1 mg/min for 6 hrs, then reduce to 0.5 mg/min for 18 hrs. Supplementary boluses of 150 mg can be repeated every 10 min as necessary for recurrent or resistant arrhythmias. |
| Atropine     | Symptomatic bradycardia                               | 0.5 mg i.v. or i.o.                    | IIa                  | Maximum dose of 3 mg.  |
|              | Asystole  | 1 mg i.v. or i.o.                      | Indeterminate        | Repeat every 3–5 min, 3 mg maximum.  |
|              | PEA   | 1 mg i.v. or i.o.                      | Indeterminate        | Repeat every 3–5 min, 3 mg maximum, only indicated if rate is slow.  |
| Diltiazem    | Atrial fibrillation                                   | 0.25 mg/kg                             | IIa                  | May repeat dose in 15–20 min at 0.35 mg/kg. Administer over 2 min. Bolus is followed by infusion at 5–15 mg/hr.  |
|              | SVT   | 0.25 mg/kg                             | IIb                  | May repeat dose in 15–20 min at 0.35 mg/kg. Administer over 2 min. Bolus is followed by infusion of 5–15 mg/hr.  |
| Dopamine     | Symptomatic bradycardia                               | 2–10 µg/kg/min                         | IIb                  | Administer as a continuous infusion.   |
| Epinephrine  | Pulseless VT or VF                                    | 1 mg i.v. or i.o.                      | IIb                  | Repeat every 3–5 min.  |
|              | Symptomatic bradycardia                               | 2–10-µg/min infusion                   | IIb                  | Administer as a continuous infusion.   |
|              | PEA   | 1 mg i.v. or i.o.                      | IIb                  | Repeat every 3–5 min.  |
|              | Asystole  | 1 mg i.v. or i.o.                      | IIb                  | Repeat every 3–5 min.  |
| Ibutilide    | Atrial fibrillation                                   | 1 mg if ≥ 60 kg, 0.01 mg/kg if < 60 kg | IIb                  | Administer over 10 min. Dose may be repeated 10 min after completion of first dose.  |
| Lidocaine    | Pulseless VT or VF                                    | 1–1.5 mg/kg i.v. or i.o.               | Indeterminate        | Repeat doses of 0.5–0.75 mg/kg may be given every 5–10 min (maximum dose of 3 mg/kg). Continuous-infusion rate is 1–4 mg/min.  |
|              | Stable VT   | 0.5–0.75 mg/kg i.v. or i.o.            | Indeterminate        | Repeat doses of 0.5–0.75 mg/kg may be given every 5–10 min (maximum dose of 3 mg/kg). Continuous-infusion rate is 1–4 mg/min.  |
| Magnesium    | Pulseless VT or VF associated with torsade de pointes | 1–2 g i.v. or p.o.                     | IIa                  | If pulse absent, dilute in 10 ml of 5% dextrose in water, and administer over 5–20 min. If pulse present, mix in 50–100 ml of 5% dextrose in water, and administer over 5–60 min.  |
| Procainamide | Stable VT   | 20 mg/min                              | IIa                  | Administer until arrhythmia is suppressed, hypotension occurs, QRS widens > 50% from baseline, or total of 17 mg/kg has been administered. Maintenance infusion rate is 1–4 mg/min.  |

pulseless ventricular tachycardia or fibrillation, asystole, and PEA.<sup>25</sup> However, it has also been

suggested that epinephrine may not exert beneficial effects, with a possible association with

Table 2. The 2005 Advanced Cardiac Life Support Classification of Drugs for Specific Indications<sup>5</sup> (continued)

| Drug                     | Rhythm Indication                    | Dose             | Class Recommendation | Comments   |
|--------------------------|--------------------------------------|------------------|----------------------|--|
| Procainamide (continued) | Atrial fibrillation                  | 20 mg/min        | Not rated            | Administer until arrhythmia is suppressed, hypotension occurs, QRS widens > 50% from baseline, or total of 17 mg/kg has been administered. Maintenance infusion rate is 1–4 mg/min. Avoid use in patients with impaired left ventricular function. |
| Vasopressin              | Pulseless VT or VF, PEA, or asystole | 40 U i.v or i.o. | Indeterminate        | May be given once. May replace first or second dose of epinephrine.  |
| Verapamil                | SVT                                  | 2.5–5 mg i.v.    | IIa                  | Administer over 2 min. Dose of 5–10 mg may be repeated in 15–30 min (total dose 20 mg). Alternative dosing is 5 mg every 15 min (total dose 30 mg).  |

SVT = supraventricular tachycardia; VT = ventricular tachycardia; VF = ventricular fibrillation; i.o. = intraosseous; PEA = pulseless electrical activity.

diminished rates of resuscitation, reduced occurrences of survival to hospital discharge, or increases in the rate of postresuscitation mortality.<sup>29, 32, 33</sup>

The optimum dose of epinephrine has been a topic of considerable controversy. The original recommended dose of epinephrine in ACLS was 0.5–1 mg every 5 minutes.<sup>34</sup> However, continued low survival rates in the late 1980s and anecdotal observations in case reports of success with use of higher doses suggested the need to reevaluate dosing recommendations.<sup>34, 35</sup> The effectiveness of a higher dose of epinephrine, greater than 5 mg or 0.1 mg/kg, was compared with a standard dose of 1 mg in both the in-hospital and out-of-hospital settings.<sup>36–43</sup> Higher epinephrine doses appeared to be associated in some trials with a slight increase in rates of resuscitation, but at a cost of a higher frequency of postresuscitation complications mediated by  $\beta$ -adrenergic effects, including increased myocardial oxygen consumption and metabolic demand that may predispose patients with underlying myocardial ischemia to cardiac dysfunction and arrhythmias.<sup>42, 43</sup> Intrapulmonary shunting associated with epinephrine as a result of vasoconstriction of the pulmonary vasculature may lead to further hypoxia.<sup>44</sup> Higher epinephrine doses may increase the frequency of adverse neurologic outcomes, with longer duration of hospitalization.<sup>30, 45</sup> With the exception of selected observations in patients with asystole, pooled odds ratios of survival to hospital discharge in meta-analyses of trials comparing standard-dose with high-dose epinephrine show a trend favoring the standard 1-mg dose.<sup>30, 46, 47</sup> Although

the optimum dose or approach for epinephrine in pulseless situations (ventricular fibrillation, asystole, PEA) has not been clearly established, a dose of 1 mg is usually recommended.<sup>5, 8, 30</sup>

Current guidelines recommend intervals of 3–5 minutes between epinephrine doses.<sup>5, 8</sup> Whether the optimum interval for continued pharmacologic effects associated with intravenous epinephrine doses of 1 mg is 3 or 5 minutes is unclear. Unfortunately, in practice, intervals between epinephrine doses in patients with cardiac arrest frequently exceed 5 minutes. A mean interval of 6.5 minutes between epinephrine doses in patients with cardiac arrest has been reported, with longer intervals occurring in the out-of-hospital setting (6.8 min) compared with intervals in the inpatient setting (5.6 min).<sup>48</sup> To avoid this, the dose should be repeated with every other defibrillation–drug administration sequence.<sup>8</sup> An alternative strategy for provision of constant catecholamine effects is administration of epinephrine by continuous infusion at a rate of 1 mg every 3–5 minutes.<sup>3, 5</sup> Selection of the epinephrine dose and mode of administration will depend on the individual presentation. For example, in the patient who has already received a significant dosage of catecholamine, the administration of 1 mg of epinephrine (per ACLS guidelines) could represent an insignificant intervention. In such situations, the patient may require very aggressive dosing well in excess of traditional dosing schemes. Higher doses may be necessary in patients with cardiac arrest due to an overdose of an adrenergic  $\beta$ -receptor blocker.

If intravenous access is not available, epinephrine may be administered by intraosseous

injections. The recommended dose for intraosseous administration is 1 mg, repeated every 3–5 minutes.<sup>5,8</sup> Endotracheal tube administration is an option if intravenous or intraosseous injection is not available. The typical endotracheal tube dose is 2–2.5 mg diluted in 10 ml of sterile water; however, recent reports suggest that endotracheal tube administration may not yield a sufficient response with equipotent doses potentially 3–10 times higher.<sup>8, 49–52</sup> The potential benefit or complications of even higher doses is unclear. Intracardiac epinephrine administration in the absence of an open chest is not recommended because of a lack of proven benefit and the potential risk of cardiac trauma.<sup>3</sup> In patients in whom the chest has been opened, the dose of intracardiac epinephrine is 0.3–0.5 mg.

Finally, epinephrine may also be considered for pharmacologic cardiac pacing in patients with symptomatic bradyarrhythmias associated with hemodynamic compromise. In this setting, epinephrine should be administered by a continuous intravenous infusion at a rate of 2–10 µg/minute.<sup>5,7</sup> Small bolus doses starting at 0.5-mg increments instead of 1 mg can be considered to avoid tachyarrhythmias until a titratable continuous infusion or pacemaker is available. For management of anaphylactic reactions, an intramuscular dose of 0.3–0.5 mg (1:1000 solution) is suggested, repeated every 15–20 minutes if no improvement is observed. Doses of 0.3–0.5 mg (3–5 ml of a 1:10,000 solution) administered intravenously over 5 minutes or a continuous infusion of 1–4 µg/minute may be considered in patients with severe reactions.<sup>5</sup>

### *Vasopressin*

Vasopressin causes peripheral vasoconstriction by stimulation of vasopressin<sub>1</sub> receptors located in the skin and skeletal muscle and vasopressin<sub>2</sub> receptors located in the mesenteric circulation, resulting in shunting of blood to vital organs. In addition, vasopressin potentiates the effects of catecholamines, thereby enhancing vasoconstriction.<sup>52</sup> The actions of vasopressin lead to greater coronary perfusion pressure during CPR, potentially improving survival.<sup>38, 53</sup> Observational data have shown that higher plasma vasopressin concentrations, which may be depressed after cardiac surgery or ventricular arrhythmias, are present in patients who experience ROSC.<sup>54</sup> Although the precise duration of effect for vasopressin is unclear, the half-life of approximately 10–20 minutes suggests that repeat dosing during a cardiac arrest is not necessary.

Early experience with vasopressin was reported in eight patients receiving ACLS with a minimum of one dose of epinephrine 1 mg before administration of vasopressin 40 U.<sup>55</sup> All eight patients experienced ROSC; three survived to hospital discharge. The same investigators subsequently reported a 2-fold increase in survival to hospital admission (70% vs 35%) in 40 patients with ventricular fibrillation who received vasopressin 40 U compared with those who received epinephrine 1 mg, but with no difference between the two groups in neurologic function at the time of hospital discharge.<sup>56</sup> In a comparison of vasopressin 40 U with epinephrine 1 mg in 200 hospitalized patients with ventricular fibrillation, ventricular tachycardia, PEA, or asystole, the rates of ROSC (60% vs 59%) and survival to 1 hour after the end of resuscitation (39% vs 35%) were similar.<sup>57</sup> Hospital discharge occurred in 12 patients (12%) receiving vasopressin versus 13 (14%) receiving epinephrine, with more than 80% of these patients maintaining a high level of measured cerebral performance.

In a large trial of 1186 patients with out-of-hospital cardiac arrest due to ventricular fibrillation, PEA, or asystole who were randomly assigned to receive vasopressin 40 U (589 patients) or epinephrine 1 mg (597 patients), with a second dose administered 3 minutes later if needed, no difference was noted between the groups in the rate of survival to hospital admission (36% vs 31%) or ROSC (25% vs 28%).<sup>11</sup> Results favoring vasopressin in rates of hospital admission (29% vs 20%,  $p=0.02$ ) and discharge (4.7% vs 1.5%,  $p=0.04$ ) in asystolic patients suggest a benefit, although no significant difference was noted in the rate of resuscitation with intact neurologic function.<sup>58</sup> Additional trials are needed to determine any benefit of vasopressin as an alternative to epinephrine.

Preliminary evidence also suggests that vasopressin may be administered through the endotracheal route.<sup>59</sup> Although studies in a canine model suggest that endotracheal vasopressin administration immediately increases diastolic blood pressure compared with endotracheally administered epinephrine, recent guidelines do not advocate the use of this route.<sup>60</sup>

Because current evidence indicates no difference in efficacy between vasopressin and epinephrine, the new guidelines recommend vasopressin 40 U administered by intravenous or intraosseous route, which may be given in place of either the first or second dose of epinephrine

in patients with pulseless ventricular tachycardia or fibrillation, asystole, or PEA.<sup>5</sup> However, due to the relative lack of data from large randomized studies, vasopressin carries a class indeterminate recommendation (Table 2).

#### *Combined Administration of Vasopressin and Epinephrine*

Animal studies and case series in humans suggest that vasopressin administered in combination with epinephrine results in similar effectiveness compared with epinephrine alone, but the combination may be associated with a slight advantage in the frequency of successful resuscitation, with minimal potential for postresuscitative complications.<sup>53, 55, 56, 61</sup> In a trial comparing the efficacy of vasopressin with epinephrine, patients in either arm requiring continued resuscitation after the initial two doses of either agent received a median epinephrine dose of 5 mg (interquartile range 2–10 mg).<sup>11</sup> Significantly higher rates of ROSC, hospital admission, and discharge were observed in those receiving vasopressin and epinephrine (373 patients) compared with those receiving epinephrine alone (359 patients). The significant benefits associated with combination therapy in the rates of hospital admission and discharge occurred in patients with asystole, whereas the benefits of combination therapy with respect to ROSC occurred in patients with ventricular fibrillation and asystole.<sup>11, 62</sup>

In consideration of the relatively small sample size, the wide confidence intervals, and the fact that this study was not designed to evaluate the benefits of combined administration of epinephrine and vasopressin, a randomized trial is needed to test this hypothesis.<sup>58</sup> In a retrospective analysis, the effects of epinephrine (~3.8 mg total) in combination with vasopressin 40 U (17 patients) or administered alone (231 patients) was investigated in patients who experienced out-of-hospital cardiac arrest due to asystole, PEA, ventricular fibrillation, or undocumented arrhythmia, where a physician was present on the scene.<sup>63</sup> The investigators concluded that a potential advantage associated with the combined administration of epinephrine and vasopressin might exist.

#### *Antiarrhythmic Agents*

Beyond defibrillation, which is the only proven intervention for achieving ROSC in patients experiencing ventricular fibrillation, antiar-

rhythmic agents have been recommended as adjunctive therapies to potentially normalize abnormally depolarizing and conducting myocardial cells. The combination of defibrillation with antiarrhythmic drug therapy may restore a rhythm that can sustain normal cardiac contraction and blood pressure. However, the potential for these agents to be proarrhythmic, alter defibrillation thresholds, or lead to cardiac insufficiency should be considered. Selection of an antiarrhythmic agent and dose depends on the rhythm, presence or absence of a pulse, and previous antiarrhythmic exposure. Antiarrhythmic agents have not been shown to improve survival to hospital discharge in patients with pulseless ventricular tachycardia or fibrillation.

#### *Amiodarone*

Parenteral amiodarone inhibits conduction through sodium, potassium, and calcium channels, and has  $\alpha$ - and  $\beta$ -blocking activity.<sup>64</sup> The recommendation for the use of intravenous amiodarone in patients with pulseless ventricular tachycardia or fibrillation is based on two trials: The Amiodarone for Resuscitation after Out-of-Hospital Cardiac Arrest Due to Ventricular Fibrillation (ARREST) trial, in which the efficacy of intravenous amiodarone 300 mg was compared with placebo in patients with ventricular fibrillation; and the follow-up Amiodarone versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation (ALIVE) trial, in which the efficacy of intravenous amiodarone 5 mg/kg (2.5-mg/kg repeat dose) was compared with that of lidocaine 1.5 mg/kg (1.5-mg/kg repeat dose) in patients with shock-resistant ventricular fibrillation.<sup>65, 66</sup> Both trials were conducted in an out-of-hospital cardiac arrest setting, with mean time to drug administration exceeding 20 minutes. In the ARREST trial, the rate of survival to hospital admission was significantly higher in patients who received amiodarone (especially those with ventricular fibrillation) compared with those receiving placebo (44% vs 34%,  $p=0.03$ ). However, no difference was noted between the groups in rate of survival to hospital discharge (13.4% vs 13.2%).<sup>65</sup> Earlier administration of either agent was associated with improved survival to hospital admission. It should be noted that the study was not designed with sufficient power to show a difference in overall survival. Based on the results of the ARREST trial, intravenous amiodarone replaced lidocaine as first-line antiarrhythmic drug therapy in the treatment

algorithm for pulseless ventricular tachycardia or fibrillation in the 2000 ILCOR guidelines.

The intent-to-treat results from the ALIVE trial suggested that intravenous amiodarone was associated with a significantly higher rate of survival to hospital admission compared with lidocaine (23% vs 12%,  $p=0.009$ ), but no significant difference between groups was reported in the rate of hospital discharge (6.4% vs 3.8%,  $p=0.32$ ).<sup>66</sup> In this trial, 24 patients (13.3%) in the amiodarone group and 11 (6.6%) in the lidocaine group experienced transient ROSC before administration of the study drug, of whom 10 and 4, respectively, were admitted to the hospital.

In a retrospective analysis of inpatients with cardiac arrest due to pulseless ventricular tachycardia or fibrillation who were treated with either lidocaine (79 patients) or amiodarone (74 patients) after the 2000 ACLS guidelines were implemented, no difference was observed between the agents in survival at 24 hours.<sup>67</sup> Of note, only 25% of patients received the correct initial dose of amiodarone, and amiodarone was administered an average 8 minutes later than was lidocaine.

In a comparison of the efficacy of vasopressin with that of epinephrine in outpatients with cardiac arrest, one group of authors reported a higher rate of admission to the hospital in patients who received concomitant intravenous amiodarone.<sup>11</sup> Nevertheless, whether any difference in outcomes exists between antiarrhythmic drug therapies in hospitalized patients with witnessed arrest is unknown, since these agents have not been compared in this population.

In the ARREST and ALIVE trials, intravenous amiodarone was diluted in 20–30 ml of volume. Dilution and slower administration of intravenous amiodarone minimize the risk for bradycardia, hypotension, and phlebitis. However, in a cardiac arrest situation with a pulseless patient, any delay in therapy should be avoided. Undiluted intravenous amiodarone 300 mg has been successfully administered into a central line as close as possible to the heart, preceded by an infusion of Ringer's lactate solution 200 ml. Using this approach in an out-of-hospital cardiac arrest setting resulted in no difference in vasopressor requirements between patients who received undiluted amiodarone and those who received no intravenous amiodarone.<sup>68</sup> Previous administration of epinephrine in most of the patients may have provided a protective effect. The current recommendation for

amiodarone therapy in patients with pulseless ventricular tachycardia or fibrillation is administration of a 300-mg intravenous bolus or a 300-mg intraosseous dose if intravenous access is not available. Amiodarone may be repeated once at a dose of 150 mg if an adequate response is not achieved. The need for dilution of intravenous amiodarone is no longer specified.<sup>5</sup> A 3-ml syringe containing amiodarone 150 mg (50 mg/ml) is now available. Another option is to administer the drug into a flowing intravenous line or to follow the bolus dose with a 10–20-ml saline flush.

After successful resuscitation after the initial intravenous bolus dose, a maintenance infusion of amiodarone should be administered at a rate of 1 mg/minute for 6 hours followed by a rate of 0.5 mg/minute for 18 hours. Due to absorption of the drug by polyvinyl chloride bags, the 24-hour infusion should be admixed in a glass bottle. A maximum concentration of 2 mg/ml has been suggested for peripheral administration in order to avoid phlebitis. Higher concentrations (up to 6 mg/ml) may be given through a central line. Endotracheal administration of amiodarone is not recommended because of its local irritating effects.<sup>69, 70</sup> Amiodarone carries a class IIb recommendation for pulseless ventricular tachycardia or fibrillation (Table 2).<sup>5</sup>

### *Lidocaine*

Lidocaine, a class 1B antiarrhythmic that acts by inhibiting ion flux through sodium channels, has been used for pulseless ventricular tachycardia or fibrillation for decades. The administration of lidocaine during cardiac arrest gained acceptance based on successful human and laboratory experiences in suppressing ventricular premature depolarizations occurring during myocardial infarction.<sup>71</sup> Prophylactic use of lidocaine for prevention of ventricular fibrillation after acute myocardial infarction should be avoided because of the potential for detrimental effects.<sup>72</sup> In terms of overall efficacy, objective data supporting the use of lidocaine in pulseless ventricular tachycardia or fibrillation are lacking.

In a retrospective analysis of 290 patients with out-of-hospital ventricular fibrillation, 185 patients received lidocaine compared with 105 patients who did not.<sup>29</sup> Significant increases were noted in the rates of ROSC (45% vs 24%,  $p<0.001$ ) and hospital admission (38% vs 18%,  $p<0.01$ ) in those who received lidocaine. No significant difference was noted between the two groups in the rate of hospital discharge (14% vs

8%). Significantly greater rates of a nurse present (47% vs 2%,  $p < 0.001$ ) and use of epinephrine (47% vs 3%,  $p < 0.001$ ) occurred in the lidocaine group. Use of epinephrine tended to be associated with reduced chance for survival; in contrast, after adjusting for independent factors, lidocaine administration was associated with improved survival.

In a randomized, unblinded study, the efficacy of lidocaine 100 mg was compared with that of epinephrine 0.5 mg in 199 patients with outpatient ventricular fibrillation.<sup>16</sup> No significant difference was noted in the rate of ROSC. However, a significantly higher proportion of individuals who received lidocaine developed asystole (25%) compared with those in the epinephrine group (7%,  $p < 0.02$ ).

As a result of a paucity of data supporting the efficacy of lidocaine for cardiac arrest, the 2000 and 2005 ACLS guidelines list lidocaine as class indeterminate in the pulseless ventricular tachycardia or fibrillation algorithm as an alternative to amiodarone (if unavailable).<sup>5</sup>

The recommended dose of lidocaine for pulseless ventricular tachycardia or fibrillation is a 1–1.5-mg/kg initial bolus administered intravenously or intraosseously, with repeated doses of 0.5–0.75 mg/kg at 5–10-minute intervals, up to a maximum of three doses or a total dose of 3 mg/kg. The 1.5-mg/kg dose was added in the 2000 guidelines to reduce the time necessary to achieve the maximum 3-mg/kg dose, before selecting an alternative agent. Lidocaine is available in a prefilled ready-to-use 100-mg syringe. After the occurrence of ROSC, a continuous infusion of 1–4 mg/minute is recommended, with a reduction in the infusion rate to 1–2 mg/minute in patients with impaired hepatic or cardiac function or low muscle mass (such as in elderly patients), to avoid neurologic adverse effects, mainly seizures.<sup>3</sup> In the absence of intravenous or intraosseous access, lidocaine may be administered through an endotracheal tube, at a dose of 2–4 mg/kg.

### *Magnesium*

When the morphology of pulseless ventricular tachycardia or fibrillation resembles that of torsade de pointes, magnesium sulfate is indicated, even in the absence of hypomagnesemia.<sup>5</sup> Hypomagnesemia can inhibit conductance through myocardial potassium channels, which leads to prolongation of the action potential duration via prolongation of ventricular

repolarization, resulting in QT-interval prolongation on the electrocardiogram. The effects of magnesium may be due to several mechanisms, including improved potassium transport through myocardial potassium channels and shortening of the action potential duration.

In a small study of 67 patients with out-of-hospital cardiac arrest, a prophylactic dose of magnesium sulfate 5 g did not result in a significant difference in the rate of ROSC compared with that associated with placebo.<sup>73</sup> Magnesium has a class IIa recommendation for torsade de pointes and should be administered as 1–2 g diluted in 10 ml of 5% dextrose in water (D<sub>5</sub>W) over 5–20 minutes. For patients with persistent pulseless ventricular tachycardia or fibrillation with known hypomagnesemia, magnesium should be administered over 1–2 minutes. Magnesium is indicated for administration during pulseless ventricular tachycardia or fibrillation in patients who have hypomagnesemia. The rate of mortality has been shown to be higher in patients experiencing cardiac arrest with serum magnesium concentrations below the target range.<sup>74</sup> A serum magnesium concentration greater than 2 mg/dl is desired in patients undergoing resuscitation of cardiac arrest.

### **Tachyarrhythmias**

The tachyarrhythmias encompass a number of rhythm disturbances, each of which requires different management depending on the presence of hemodynamic instability secondary to the rhythm, whether QRS complexes are narrow or wide ( $> 0.12$  sec), and whether the rhythm is regular or irregular. The tachyarrhythmias that occur most frequently include atrial fibrillation or flutter, paroxysmal supraventricular tachycardia (PSVT), stable wide-complex tachycardia of unknown type, and stable monomorphic or polymorphic ventricular tachycardia. Before drug therapy is started, the patient's hemodynamic stability must be assessed. A patient is considered hemodynamically unstable if hypotension (systolic blood pressure  $< 90$  mm Hg), chest pain, mental status changes, symptomatic heart failure, or other symptoms of shock are present. Hemodynamic instability is more common in a healthy heart when the ventricular rate exceeds 150 beats/minute. Patients who are hemodynamically unstable due to a tachyarrhythmia must be managed by emergent direct current cardioversion.<sup>5,8</sup>

Diagnosis and management of rapid ventricular rates as a result of supraventricular tachyarrhythmias can be challenging. If the arrhythmia is atrial fibrillation or atrial flutter, a calcium channel blocker (verapamil or diltiazem),  $\beta$ -blocker, or digoxin can be used to slow conduction through the atrioventricular node. Amiodarone administered by slow intravenous infusion or orally has been used for conversion to normal sinus rhythm in patients with acute-onset atrial fibrillation.<sup>75, 76</sup> In patients with ventricular tachycardia or tachycardia of uncertain origin, amiodarone may be administered.

### Paroxysmal Supraventricular Tachycardia

#### *Adenosine*

When a regular rate is present with a narrow QRS complex, and the source of the arrhythmia is believed to be atrioventricular nodal reentry, adenosine is considered the drug of choice (class I recommendation) for PSVT (Table 2). Adenosine temporarily inhibits conduction through the atrioventricular node, resulting in conversion to sinus rhythm. Due to its short half-life (~10 sec), the initial 6-mg dose must be given by rapid intravenous administration (over 1–3 sec) through a line in a large vein (antecubital) and immediately followed by a 20-ml saline flush while elevating the arm (if this is the location of intravenous administration) to enhance delivery to the heart. The onset of effect is usually within 1 minute (typically 15–30 sec).<sup>77</sup> If the arrhythmia is not terminated within 1–2 minutes, then a dose of 12 mg may be administered. Adenosine may be repeated a third time, at a dose of 12 mg.<sup>5</sup> Because adenosine may transiently precipitate complete atrioventricular nodal blockade, a lower starting dose of 3 mg is suggested when administered through a central infusion site.<sup>78, 79</sup> The dose of adenosine should also be reduced to 3 mg in patients who have recently undergone heart transplantation and in those taking carbamazepine or dipyridamole, as these drugs may inhibit cellular uptake and metabolism of adenosine, prolonging and potentiating the effects of the drug.<sup>5, 8, 80</sup> Theophylline and caffeine are nonspecific adenosine receptor antagonists that can inhibit the effects of adenosine at its extracellular receptor site; larger doses may be required in patients taking these drugs.

Adenosine is indicated for reentry-related sustained supraventricular tachycardia refractory to vagal maneuvers (class I); unstable supra-

ventricular tachycardia while preparing for cardioversion (class IIb); undefined, stable narrow-complex tachycardia as a treatment or diagnosis maneuver; and stable, wide-complex tachycardias when a previously defined reentry has been defined.<sup>5</sup> Some of the most common adverse effects associated with adenosine are chest pain, flushing, and dyspnea. Atrial fibrillation may be induced by adenosine in approximately 12% of patients.<sup>81</sup> Also, bradyarrhythmias, sinus pauses, and ventricular tachycardia have been reported, although less commonly.<sup>81</sup> The duration of adenosine-induced adverse effects may last from 15 seconds to several minutes or longer. If prolonged asystole occurs, atropine or epinephrine may be required. Asystole that is unresponsive to atropine and epinephrine as a result of drug accumulation may respond to an aminophylline 250-mg intravenous bolus.<sup>82</sup>

Also, adenosine has been shown to be equally effective as verapamil for conversion to sinus rhythm of PSVT.<sup>83–86</sup> Conversion typically occurs after the first dose. The onset of response associated with adenosine (a few seconds to 1 min) occurs more rapidly than with verapamil (approximately 10 min).<sup>87</sup> In addition, the frequency of hypotension associated with adenosine is lower than that due to verapamil. Another potential advantage of adenosine is the ability to aid in arrhythmia identification. For example, adenosine administration does not result in conversion of atrial fibrillation or flutter to sinus rhythm, but rather transiently slows the ventricular rate, and may uncover “flutter waves.” In contrast, adenosine usually results in conversion of PSVT to sinus rhythm.<sup>88</sup>

#### Atrial Fibrillation or Flutter

The management of atrial fibrillation or atrial flutter may involve a number of drug therapies. Initial assessment should include the hemodynamic stability of the patient, duration of the arrhythmia, presence or absence of a history of heart failure, and, if possible, the patient's left ventricular ejection fraction. The goal of therapy with atrial fibrillation or flutter is to control the ventricular rate and, subsequently, to consider conversion to sinus rhythm. If the arrhythmia is less than 48 hours in duration, then rapid cardioversion may be considered. However, if the duration of the arrhythmia is more than 48 hours, then attempts at conversion to normal sinus rhythm must be delayed until a transthoracic echocardiogram can be obtained to confirm the absence of a left

atrial thrombus, or until the patient has received therapeutic anticoagulation for at least 3 weeks.

#### *Diltiazem and Verapamil*

Diltiazem and verapamil are nondihydropyridine calcium channel blockers that inhibit extracellular calcium influx through slow calcium channels, inhibiting automaticity in the sinoatrial node and conduction through the atrioventricular node. In addition, calcium channel inhibition in smooth muscle cells results in arterial vasodilation and hypotension. Although diltiazem has less negative inotropic activity than verapamil, diltiazem has been shown to worsen heart failure in patients with left ventricular dysfunction and increases the occurrence of late-onset heart failure in patients who have experienced myocardial infarction with early reduction in ejection fraction.<sup>89</sup> Intravenous diltiazem may be less likely to cause profound hypotension than intravenous verapamil.<sup>90</sup>

The use of calcium channel blockers should be avoided in patients with atrial fibrillation or flutter associated with known preexcitation conditions such as Wolff-Parkinson-White syndrome, as these drugs may cause a paradoxical increase in ventricular response. In this setting, amiodarone should be considered at a dose of 150 mg over 10 minutes. Administering verapamil to a patient with a wide-complex rhythm can result in cardiovascular collapse and death, predominantly due to its vasodilatory properties, and is therefore contraindicated in this setting. Both diltiazem and verapamil administered intravenously carry a class IIa recommendation for use in patients with atrial fibrillation or flutter. Recommended doses are provided in Table 2.

#### *β-Blockers*

The benefits of β-blockers for ventricular rate control in patients with atrial tachyarrhythmias and the cardioprotective effects of these agents in patients with acute coronary syndromes are well established and are affirmed in the 2005 guidelines. If a patient has a narrow-QRS complex tachycardia such as PSVT that is uncontrolled by vagal maneuvers, then adenosine, calcium channel blockers, or a β-blocker such as atenolol, metoprolol, propranolol, or esmolol may be administered.<sup>8</sup> If atrial fibrillation or flutter is due to Wolff-Parkinson-White syndrome, use of a β-blocker may favor the alternative pathway and lead to ventricular arrhythmias.

The use of β-blockers is contraindicated in the presence of second-degree or third-degree atrioventricular block, severe lung disease with bronchospasm, hypotension, or decompensated heart failure.<sup>8</sup> Combined use of β-blockers with calcium channel blockers should be performed with the knowledge that cardiovascular effects could be additive. Propranolol is contraindicated in cocaine-induced acute coronary syndromes.<sup>5</sup> Recommended doses of β-blockers are presented in Table 3.

#### *Digoxin*

In view of the narrow therapeutic index of digoxin, the risk for adverse effects, and the slow onset of action, digoxin administration should be avoided in emergency cardiovascular care.<sup>5</sup> It can be considered, however, for rhythm control in patients with atrial fibrillation of less than 48 hours' duration.

#### *Amiodarone*

Intravenous amiodarone is effective for conversion to normal sinus rhythm of atrial fibrillation of 48 hours' or less duration.<sup>91</sup> Amiodarone may be administered for termination of atrial fibrillation and for subsequent maintenance of sinus rhythm (Table 2).<sup>5</sup>

#### *Ibutilide*

Ibutilide is a potassium channel-inhibiting antiarrhythmic agent that can be used to convert atrial fibrillation or flutter of less than 48 hours' duration to normal sinus rhythm (class IIb). Before administration of ibutilide, hypomagnesemia and hypokalemia should be corrected, and the use of other class III agents avoided within 4 hours to reduce the risk of ibutilide-induced torsade de pointes.<sup>92</sup> In patients weighing 60 kg or more, the recommended dose is 1 mg. In patients weighing less than 60 kg, the recommended dose is 0.01 mg/kg (Table 2).<sup>5, 92</sup> A second dose equal to the first may be administered 10 minutes after completion of the first dose if the arrhythmia has not terminated. Administration of ibutilide should be considered only if the duration of atrial fibrillation or atrial flutter is 48 hours or less. In addition, ibutilide should be used with caution in patients with left ventricular dysfunction; it should be avoided in patients with left ventricular ejection fraction less than 20% and in patients with a rate-corrected QT interval exceeding 440 msec.

Table 3. Recommended Dosages of  $\beta$ -Blockers<sup>5</sup>

| $\beta$ -Blocker | Selectivity        | Dose  | Administration Time           | Repeat Interval   |
|------------------|--------------------|---|-------------------------------|---|
| Atenolol         | $\beta_1$          | 5 mg  | 5 min                         | 10 min  |
| Metoprolol       | $\beta_1$          | 5 mg  | 2 min                         | 5 min; may give up to 2 more doses (maximum total dose of 15 mg)  |
| Propranolol      | $\beta_1, \beta_2$ | 0.1 mg/kg in 3 divided doses  | 1 mg/min (maximum)            | Administer each divided dose every 2–3 min  |
| Esmolol          | $\beta_1$          | 500- $\mu$ g/kg i.v. loading dose, then 50- $\mu$ g/min infusion over 4 min | Loading dose given over 1 min | If inadequate response, then administer a second bolus of 0.5 mg/kg over 1 min, and increase infusion rate to 100 $\mu$ g/kg; maximum dosage 300 $\mu$ g/kg/min |

### Wide-Complex Tachycardias

A wide-complex tachycardia is defined as a tachyarrhythmia in which the QRS complex is 0.12 second or more. Several arrhythmias fall into this category, including ventricular tachycardia, preexcitation tachycardias, PSVT with aberrant conduction, and torsade de pointes.

#### Amiodarone

Evidence supports the effectiveness of amiodarone to terminate drug-refractory or shock-resistant ventricular tachycardia (class IIb).<sup>93–95</sup> For the management of hemodynamically stable ventricular tachycardia with pulse, the recommended dose of intravenous amiodarone is 150 mg, diluted in 100 ml of D<sub>5</sub>W, to be administered over 10 minutes or longer to reduce potential for hypotension or bradycardia (Table 2).<sup>3, 5</sup> Vasodilation observed with amiodarone administration is primarily caused by the diluent, polysorbate 80, which can be minimized by slowing the infusion rate. The 24-hour infusion (mixed in glass) rate and dose of intravenous amiodarone is the same for both pulseless ventricular tachycardia or fibrillation and stable ventricular tachycardia.

#### Procainamide

Procainamide inhibits the flux of ions through sodium channels. In addition, an active metabolite, *N*-acetylprocainamide, inhibits ion flux through potassium channels. Procainamide has been used for the management of pulseless ventricular tachycardia or fibrillation, PSVT, and sustained ventricular tachycardia, although its use is typically reserved for patients with stable ventricular tachycardia or those with recurrent ventricular tachycardia unresponsive to other antiarrhythmic agents. Procainamide should be

administered only to patients with preserved left ventricular function, because of negative inotropic effects and the potential for hypotension.

When used in stable ventricular tachycardia, an infusion rate of 20 mg/minute (to a total dose of 1 g) is suggested to reduce the risk of hypotension, QRS prolongation that may lead to ventricular tachycardia, or torsade de pointes. After the initial bolus of 1 g, a maintenance infusion of 1–4 mg/minute is recommended if continuation of the drug is desired.<sup>5</sup> Lower infusion rates (1–2 mg/min) should be considered in the setting of renal or hepatic insufficiency. Current guidelines recommend the use of procainamide in stable monomorphic ventricular tachycardia (class IIa, Table 2) or to control rhythm in patients with atrial fibrillation and preserved left ventricular function.<sup>5</sup>

The 2005 ACLS guidelines no longer recommend the use of procainamide in the setting of pulseless ventricular tachycardia or fibrillation because supportive data regarding the efficacy of procainamide for this indication are very limited.<sup>8, 96</sup> In an analysis of the effects of six different drug therapies (atropine, bretylium, calcium, lidocaine, procainamide, and sodium bicarbonate) in 529 inpatients or outpatients, 50% of the 20 patients receiving procainamide (8 of 16 with ventricular tachycardia or fibrillation, 1 of 2 with PEA, and 1 of 2 with asystole) were resuscitated.<sup>97</sup> Lower long-term survival rates were associated with procainamide compared with those resulting from no antiarrhythmic or  $\beta$ -blocker administration ( $p < 0.001$  for survival) in patients undergoing resuscitation of prehospital cardiac arrest due to ventricular fibrillation.<sup>98</sup>

Procainamide administration may be considered for patients who have been resuscitated but remain unstable, requiring repeated defibrillations despite the administration of amiodarone or

lidocaine. In this situation, procainamide should be administered as a loading dose of 1 g intravenously at a rate of 20–50 mg/minute. The maximum dose is 17 mg/kg. The loading dose must be diluted before administration, thereby prolonging the time for onset of action.

#### *Lidocaine*

Lidocaine is indicated for the management of hemodynamically stable monomorphic ventricular tachycardia in patients with preserved left ventricular function (class indeterminate; Table 2), but alternative agents (amiodarone and procainamide) are preferred.<sup>5</sup> The initial recommended lidocaine dose is 0.5–0.75 mg/kg administered as an intravenous bolus. This dose can be repeated in 5–10 minutes, if necessary, to a total dose of 3 mg/kg.

#### Torsade de Pointes

##### *Magnesium*

Magnesium is indicated for the termination of hemodynamically stable torsade de pointes. The use of magnesium to treat torsade de pointes is based on uncontrolled small case series. One of the larger series described 12 patients with prolonged QT interval who developed torsade de pointes.<sup>99</sup> Administration of magnesium sulfate as a single 2-g intravenous bolus resulted in termination of torsade de pointes in 9 patients; a repeat dose 5–15 minutes later was required to terminate the rhythm in the other patients. In eight individuals with polymorphic ventricular tachycardia and a normal QT interval, no response was observed, suggesting that magnesium may not be effective when the QT interval is normal.<sup>5,99</sup>

The routine use of magnesium for prophylaxis in normomagnesemic patients with acute myocardial infarction or refractory ventricular fibrillation is not recommended.<sup>8,100,101</sup> However, it is prudent to measure serum magnesium concentrations in hospitalized patients who may be at risk for developing cardiac arrhythmias and to administer magnesium to correct hypomagnesemia. Current guidelines recommend administration of magnesium 1–2 g diluted in D<sub>5</sub>W and administered over 5–60 minutes.<sup>5</sup>

#### **Asystole, Pulseless Electrical Activity, Symptomatic Bradycardia**

Several approaches can be used to manage symptomatic bradycardia. This includes use of

an internal or external pacemaker or drug therapy, either by increasing the rate of conduction by stimulating  $\beta_1$ -adrenergic activity with catecholamines or by blocking parasympathetic activity with atropine.

#### Atropine

Atropine inhibits cholinergic responses that diminish heart rate and systemic vascular resistance, and is recommended for use in patients with symptomatic bradycardia, PEA with bradycardia, and asystole.<sup>5</sup> Supporting data are limited and unclear in terms of the effectiveness of atropine for asystole. One small prospective study in 21 patients found no significant difference in the rate of successful resuscitation in patients who received atropine and in those who did not (control group).<sup>102</sup> A large retrospective analysis in 170 patients with asystole that was resistant to epinephrine found a significantly higher rate of resuscitation associated with atropine (14%) compared with placebo (0%).

The recommended dose of atropine for the management of asystole or PEA associated with bradycardia is 1 mg intravenously, repeated every 3–5 minutes, for a maximum dose of 3 mg.<sup>5</sup> The ILCOR guidelines suggest a single 3-mg intravenous dose in patients with asystole or PEA associated with bradycardia.<sup>8</sup> Doses exceeding the maximum may result in total vagal blockade. For the management of symptomatic bradycardia, the recommended dosage is 0.5 mg every 3–5 minutes (3 mg maximum).<sup>5,8</sup> Higher doses, starting at 2–4 mg, are suggested if an organophosphate, carbamate, or nerve agent poisoning is present.<sup>5</sup> Slow infusions of atropine or individual doses less than 0.5 mg should be avoided, as these have been associated with a paroxysmal parasympathetic response, further slowing the heart rate and exacerbating the bradycardia.<sup>6</sup>

Atropine administration in the presence of second-degree atrioventricular block Mobitz type II should be performed cautiously because of the theoretic potential for atropine to exacerbate the atrioventricular block by accelerating the atrial rate.<sup>3,6,5</sup> Atropine should be used with caution in patients with acute coronary syndromes, secondary to potential increases in ischemia and zone of infarction from elevated heart rates.<sup>5</sup> Atropine should also be used cautiously in patients with denervated hearts after transplantation. There is some limited evidence suggesting that aminophylline may be a promising

adjunct in patients with atropine-resistant atrioventricular block (250 mg intravenously over 10 min) or atropine-resistant asystole (250-mg intravenous bolus).<sup>81, 103</sup> Atropine 2–2.5 mg may be administered through an endotracheal tube if intravenous access is not available. Atropine carries a class IIa recommendation for symptomatic bradycardia and class indeterminate for asystole after three doses have been administered (Table 2).

### Hyperkalemia and Hypokalemia

Potassium is a predominantly intracellular electrolyte that is essential for nerve transmission, cardiac muscle contraction, renal function, protein synthesis, and carbohydrate metabolism.<sup>104</sup> Significant changes in serum potassium concentrations, either too high or too low, may result in life-threatening arrhythmias. Hyperkalemia (potassium concentration > 5 mEq/L) may result from a variety of causes, including chronic kidney disease, drugs, tumor lysis syndrome, hypoaldosteronism, diet, and metabolic acidosis. Electrocardiographic changes associated with hyperkalemia include peaked T waves, prolonged PR interval, and wide QRS complex.

Treatment of hyperkalemia involves assessment of the patient's clinical presentation, as well as identification and resolution of any causes of hyperkalemia, including the following drugs: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists,  $\beta$ -blockers, heparin, potassium supplements, penicillin derivatives, and nonsteroidal antiinflammatory drugs. Initial therapy may include the use of loop diuretics (furosemide 40–80 mg intravenously) and binding resins such as sodium polystyrene sulfonate (15–30 g diluted in 50–100 ml of sorbitol [20%] administered orally or rectally) to facilitate removal of potassium from the body.<sup>5</sup> However, these methods reduce serum potassium concentrations relatively slowly. If serum potassium concentrations are moderate (6–7 mEq/L) or critically high (> 7 mEq/L), especially with electrocardiographic changes of concern, methods to shift potassium into cells should be undertaken. The recommended therapy in this situation is D<sub>5</sub>W 250 g (50 ml), followed by regular insulin 10 U administered intravenously over 15–30 minutes, and calcium chloride (10%) 500–1000 mg (5–10 ml) intravenously over 2–5 minutes. Calcium may be sequentially adminis-

tered to stabilize the myocardium and minimize the effects of potassium on the myocyte. Sodium bicarbonate 50 mEq intravenously over 5 minutes or nebulized albuterol 10–20 mg over 15 minutes may also shift potassium intracellularly.<sup>5</sup> These drugs are often administered sequentially.<sup>5</sup> Shifting potassium into the cell is a temporary means of reducing serum potassium concentrations. If this combination of drugs is administered, methods to remove potassium from the body with diuretics, sodium polystyrene sulfonate, or hemodialysis should be undertaken.

Hypokalemia (potassium concentration < 3.5 mEq/L) may result from diarrhea, laxatives, diuretics, antibiotics, elevated blood glucose concentrations, or hyperaldosteronism. The myocardial effects of low serum potassium concentration include a reduction in cardiac tissue excitability and conduction. Electrocardiographic findings may include T-wave flattening, QT-interval prolongation, ventricular arrhythmias, PEA, or asystole. Treatment of hypokalemia requires correcting any mechanism of potassium loss in addition to either intravenous or oral potassium replacement, depending on the severity of symptoms. The rate of replacement should not exceed 10 mEq/hour when administered through a peripheral intravenous catheter or 20 mEq/hour when administered through central access. If rapid replacement is necessary in patients with hypokalemia and cardiac arrest, potassium 10 mEq could be administered over 5 minutes; the dose may be repeated once.<sup>5</sup>

### Sodium Bicarbonate

Acidosis occurs frequently in patients with circulatory collapse and respiratory failure because of the accumulation of hydrogen ion and carbon dioxide. According to the hemoglobin dissociation concept, decreased pH (acidosis) results in reduced binding of oxygen to hemoglobin, ultimately reducing oxygen delivery to the tissues. In contrast, elevated pH (alkalosis) is associated with increased binding of oxygen to hemoglobin. At a pH of 7.5 or greater, tight binding of oxygen to hemoglobin results in greater reduction of oxygen delivery to tissues compared with that which occurs in the setting of a low pH. Thus, it is important to strike a balance to enable adequate oxygen transport to the tissues. Early guidelines for management of pulseless ventricular tachycardia or fibrillation recommended sodium bicarbonate as a primary mode of therapy. However, the resultant high pH

values raised concern for the potential for harmful effects.<sup>6</sup> Administration of sodium bicarbonate has shown no beneficial effect on survival, and may worsen survival probability.<sup>105, 106</sup> pH values exceeding 7.55 at 10 minutes during cardiac arrest were associated with a decreased rate of survival.<sup>107</sup>

Additional concerns regarding the use of sodium bicarbonate include data suggesting possible alteration in defibrillation thresholds, compromised coronary perfusion pressures, creation of a hyperosmolar state, hypernatremia, central venous acidosis, and inactivation of administered catecholamines.<sup>108</sup> It has also been postulated that in the presence of poor air exchange, carbon dioxide accumulation may occur. This can lead to passive diffusion of carbon dioxide into myocytes, causing intracellular hypercarbia and acidosis, which may disrupt cellular metabolism.<sup>109, 110</sup> As a result of these concerns, the routine use of sodium bicarbonate in the absence of documented metabolic acidosis or hyperkalemia is no longer advocated.<sup>5, 111</sup>

There may be a role for sodium bicarbonate administration in the setting of preexisting metabolic acidosis or hyperkalemia and in phenobarbital or tricyclic antidepressant overdose, in order to alkalinize the urine for facilitation of drug clearance.<sup>5</sup> In these clinical situations, the typical dose is 1 mEq/kg, followed by arterial blood gas monitoring to guide the administration of subsequent doses. Sodium bicarbonate should not be administered through the same intravenous access site as calcium chloride, as precipitation resulting in the formation of calcium carbonate may occur, which may occlude the tubing.

## Calcium

Calcium is a critical ion necessary for contraction of muscle tissue and cardiac conduction, enzymatic reactions, platelet aggregation, and receptor activation. Calcium is important for the treatment of both hyperkalemia and hypermagnesemia, as it moderates the effects of potassium perturbations at the cell membrane. Hypocalcemia is defined as a serum calcium concentration below 8.5 mg/dl or an ionized calcium concentration below 4.2 mg/dl. Hypercalcemia is defined as a serum calcium concentration above 10.5 mg/dl or ionized calcium concentration above 4.8 mg/dl. Serum calcium concentrations are directly related to

serum albumin concentrations. For every 1-g/dl change in serum albumin concentration, serum calcium concentrations correspondingly change by 0.8 mg/dl.

In the presence of low serum calcium concentrations, smooth muscle contraction may not be sufficient to maintain adequate pressures. The use of plasma expanders, catecholamine infusions, and adequate volume replacement may not elicit a sufficient hemodynamic response in the presence of hypocalcemia, necessitating parenteral calcium replacement. The recommended means of calcium replacement in patients with hypocalcemia is calcium gluconate 1 g (10%), 10–20 ml intravenously over 10 minutes. This should be followed by a continuous infusion of calcium gluconate using 58–77 ml of a 10% solution (yielding 540–720 mg of elemental calcium) mixed in either 500 or 1000 ml to infuse at a rate of 0.5–2 mg/kg/hour.<sup>5</sup> Calcium chloride may also be administered at a dose of 5 ml of a 10% solution over 10 minutes, followed by 1 g over the next 6–12 hours.<sup>5</sup>

The recommended dose of calcium chloride in life-threatening situations before the 2005 guidelines was 2–4 mg/kg, but the dose was recently increased to 8–16 mg/kg for unspecified reasons.<sup>3, 5</sup> Prefilled calcium syringes typically contain 1 g of calcium chloride, which is approximately 14 mg/kg. When administering calcium chloride to a patient with a pulse, a 1-g (10%) dose should be administered at a rate not to exceed 1 ml/minute. Serum calcium concentrations should be monitored every 4–6 hours. In patients with cardiac arrest to whom calcium chloride 500 mg was administered, initial mean serum calcium concentrations were 15.3 mg/dl (range 12.9–18.2 mg/dl), which declined to 11.2 mg/dl at 10 minutes; serum calcium concentrations were normal at 15 minutes.<sup>112</sup>

Hypercalcemia can lead to neurologic symptoms such as depression, confusion, and fatigue. Critically high serum calcium concentrations can lead to hallucinations, seizures, and coma. Management of hypercalcemia includes the administration of fluids, such as normal saline infused at 300–500 ml/hour to a goal urine output of 200–300 ml/hour, to facilitate calcium excretion and restore intravascular volume. Additional therapies include hemodialysis, which may be considered when volume administration is precluded due to heart failure or kidney disease. When administering these therapies, serum magnesium and potassium concentrations should be followed closely.

Calcium administration during cardiac arrest has not been associated with benefit and may lead to detrimental outcomes.<sup>97, 113, 114</sup> In a retrospective analysis of 129 patients with asystole, the rate of survival was significantly lower in patients who received calcium 0.5–1 g (8%) compared with those that received no calcium (33%).<sup>115</sup> Current recommendations do not advocate the administration of calcium chloride in the absence of hyperkalemia, hypocalcemia, or calcium channel blocker overdose.<sup>3</sup>

### Hypotension

Hypotensive patients may require a continuous infusion of an inotrope or vasopressor for hemodynamic support. Typical options include epinephrine, dopamine, dobutamine, phenylephrine, norepinephrine, or vasopressin. Dobutamine 5–20  $\mu\text{g}/\text{kg}/\text{minute}$  is usually preferred for patients with hypotension due to severe heart failure, as the drug increases myocardial contractility by stimulation of  $\beta_1$ -receptors without increasing vascular resistance. Agents with combined  $\alpha$ - and  $\beta$ -adrenergic effects (dopamine, epinephrine, and norepinephrine) may be preferred in the presence of combined hypotension and bradycardia. Dopamine is available in premixed bags, allowing rapid turnaround from request to infusion. Dopamine at dosages of 5–20  $\mu\text{g}/\text{kg}/\text{minute}$  trigger the presynaptic release of norepinephrine. However, once presynaptic norepinephrine stores are depleted, effects may be diminished. In contrast, norepinephrine 0.5–1.0  $\mu\text{g}/\text{minute}$  (titrated to effect) stimulates postsynaptic receptors, with more potent agonism of  $\alpha$ -receptors, making it preferable for use in patients with severe hypotension. Higher norepinephrine dosages of 8–30  $\mu\text{g}/\text{minute}$  may be required in patients with refractory shock. Data supporting the use of norepinephrine in patients with cardiac arrest are limited but suggest that it may be equally effective as epinephrine.<sup>41, 116</sup>

Hypotension as a result of peripheral vasodilation may be more responsive to agents that stimulate peripheral  $\alpha$ -receptors to increase arterial vascular resistance. Phenylephrine has pure  $\alpha_1$ -adrenergic effects, potentially avoiding harmful influences of  $\beta$ -adrenergic stimulation. However,  $\alpha_1$ -receptors may rapidly desensitize in patients with acute myocardial infarction. In addition, stimulation of  $\alpha_1$ -receptors in the myocardium may elicit inotropic and chronotropic

effects similar to those associated with  $\beta$ -receptor stimulation, which may potentiate ischemic damage.<sup>117</sup> This may explain the diminished effectiveness of the pure  $\alpha_1$ -agonists methoxamine and phenylephrine compared with that of epinephrine in prolonged cardiac arrest.<sup>118</sup> Future potentially beneficial options in cardiac arrest that require study include peripheral vasoconstriction by selective  $\alpha_2$ -agonists.

The use of short-term continuous vasopressin infusions of 0.01–0.04 U/minute is also gaining some interest for patients with catecholamine resistance, cardiogenic shock, or severe septic shock.<sup>119–122</sup> In patients with septic shock, a lower dosage of vasopressin of 0.2–0.4 U/minute is recommended for physiologic replacement. Higher dosages have been associated with myocardial infarction, ischemia, decreased cardiac output, and cardiac arrest.<sup>121</sup>

### Pulmonary Embolism

Pulmonary embolism is associated with a mortality rate of approximately 15%.<sup>123</sup> The presence of shock or hemodynamic instability in patients with pulmonary embolism at presentation portends an even worse prognosis, with mortality rates of more than 50%.<sup>124</sup> Massive pulmonary embolism can also deteriorate into cardiac arrest, which is most commonly manifested as either PEA or asystole, in nearly 40% of cases.<sup>125</sup> Although patients with hemodynamically stable pulmonary embolism can be managed successfully in the acute setting with anticoagulants, patients with pulmonary embolism and concomitant hemodynamic instability (e.g., systolic blood pressure  $\leq 90$  mm Hg, those requiring CPR, or those in cardiogenic shock) at presentation who are at low risk for bleeding may be considered candidates for thrombolytic therapy.<sup>126</sup>

### Thrombolytic Therapy

Discussion of the vast body of evidence regarding the use of thrombolytic agents for the treatment of ST-segment elevation myocardial infarction is beyond the scope of this article and is the topic of excellent reviews.<sup>127–129</sup> Since an initial positive case report with use of streptokinase in 1964,<sup>130</sup> a number of small randomized clinical trials have evaluated the safety and efficacy of streptokinase, urokinase, and alteplase in patients with pulmonary embolism.<sup>131–138</sup> In one of the largest trials, 160 patients with angiographically documented

pulmonary embolism were randomly assigned to receive a 12-hour intravenous infusion of urokinase or unfractionated heparin (UFH).<sup>139</sup> Although urokinase was associated with more rapid (but incomplete) resolution of pulmonary embolism compared with heparin at 24 hours, the benefits were not sustained. No significant difference was noted between the groups in the rate of mortality or recurrent pulmonary embolism. Comparable resolution of pulmonary embolism at 24 hours and similar mortality rates at 2 weeks were reported in association with a 24-hour infusion of streptokinase and a 12-hour infusion of urokinase.<sup>132</sup>

In a study of hemodynamically stable patients with pulmonary embolism, 101 patients were randomly assigned to receive alteplase 100 mg over 2 hours followed by UFH, or UFH alone.<sup>136</sup> Although a relatively rapid and significant improvement in right ventricular function and lung perfusion was noted at 24 hours with the combination of alteplase and UFH, these did not translate into clinical benefit, since the rate of recurrent pulmonary embolism within 14 days was not significantly different between the groups. In the prospective, randomized Management Strategies and Prognosis of Pulmonary Embolism-3 (MAPPET-3) trial, 256 hemodynamically stable patients with acute, submassive pulmonary embolism and evidence of right ventricular dysfunction or pulmonary hypertension received concomitant alteplase 100 mg over 2 hours and UFH or UFH alone.<sup>138</sup> The primary end point of death or escalation of therapy, which was defined as the need for catecholamine infusion, open-label thrombolysis, endotracheal intubation, CPR, or emergency embolectomy, occurred in significantly fewer patients in the alteplase group (11%) than in the group who received UFH alone (25%). The reduction was primarily attributed to the reduced need to escalate therapy in the alteplase group; the incidence of mortality was similar between the groups.

These trials are limited by relatively small sample sizes and use of surrogate end points to demonstrate efficacy, rather than mortality, as the primary outcome. Application to the setting of cardiac arrest is limited, since the enrolled patients were primarily hemodynamically stable. Although a number of published case reports and case series have described favorable outcomes with the use of thrombolytic agents during cardiac arrest in patients with massive pulmonary embolism, clinical trials are needed to evaluate

the efficacy and safety of thrombolytics in this setting.<sup>128</sup> Historically, CPR has been perceived as a relative contraindication for the use of thrombolytics because of the potentially high risk for bleeding.<sup>127</sup> However, this recommendation is not substantiated by data from clinical trials. In fact, based on available evidence, there does not appear to be a significantly increased risk of bleeding complications associated with the administration of thrombolytic therapy during CPR.<sup>140</sup>

All patients considered for thrombolytic therapy should be assessed for contraindications in order to evaluate the potential risks and benefits of therapy. The contraindications to thrombolytic therapy for pulmonary embolism are the same as those for ST-segment elevation myocardial infarction and are as follows<sup>127</sup>:

- Neurologic impairment is minor or symptoms are rapidly improving
- History of intracranial hemorrhage
- Active internal bleeding within the last 3 weeks
- Platelet count below  $100 \times 10^3/\text{mm}^3$
- Patient received heparin within the last 48 hours with an activated partial thromboplastin time greater than the upper limit of normal
- Recent warfarin use with prothrombin time greater than 15 seconds (international normalized ratio  $> 1.7$ )
- Major surgery within last 2 weeks
- Lumbar puncture within last week
- Witnessed seizure at onset of stroke
- Known arteriovenous malformation, neoplasm, or aneurysm
- Uncontrolled hypertension (systolic blood pressure  $> 185$  mm Hg or diastolic  $> 110$  mm Hg)
- Recent acute myocardial infarction
- Previous stroke within last 3 months
- Intracranial surgery or serious head trauma within 3 months
- Recent arterial puncture at a noncompressible site

Although bleeding is always a concern regarding thrombolytic therapy, the most feared complication is intracranial hemorrhage. Pooling of data from 14 clinical trials of the use of alteplase revealed an intracranial hemorrhage rate of 2.1% and a rate of fatal intracranial hemorrhage of 1.6%.<sup>141</sup> Analysis of data from a prospective registry of 2454 patients treated with either a thrombolytic or UFH found the rate of

intracranial hemorrhage associated with thrombolytic therapy to be 3%.<sup>126</sup> A recent analysis of eight randomized controlled trials with a total of 679 participants did not indicate any advantage of thrombolytic therapy over heparin.<sup>142</sup> These data provide additional insight into the potential risks of thrombolytic therapy for patients with pulmonary embolism in clinical practice.

Although several dosage regimens of alteplase have been evaluated in clinical trials, the dose approved by the United States Food and Drug Administration (FDA) for the treatment of pulmonary embolism is 100 mg administered as a continuous infusion over 2 hours. In contrast to the management of ST-segment elevation myocardial infarction, UFH is usually not administered concomitantly with thrombolytic agents, to minimize the development of bleeding complications until completion of the thrombolytic infusion.<sup>143</sup> If thrombolytic therapy is considered for cardiac arrest secondary to a pulmonary embolism, continued CPR in excess of 60 minutes may be considered before terminating resuscitation efforts.<sup>8</sup>

### Acute Ischemic Stroke

Stroke is the third leading cause of death in the United States and the most common reason for permanent disability.<sup>144</sup> Approximately 85% of all strokes are classified as ischemic, most commonly from cerebral artery occlusion due to a thrombus or embolism.<sup>145</sup>

### Thrombolytic Therapy

The rationale for administering thrombolytic therapy to select patients with acute ischemic stroke is to achieve rapid dissolution of the occlusive clot to restore cerebral blood flow and salvage viable cerebral tissue. Currently, alteplase is the only thrombolytic agent that is FDA approved for the treatment of acute ischemic stroke.<sup>146</sup> However, use of this drug requires prompt and thorough assessment of the patient to maximize its efficacy and safety.

Although four major randomized trials have evaluated the use of alteplase for acute ischemic stroke, FDA approval of this drug was based primarily on data from the National Institute of Neurologic Disorders and Stroke (NINDS) study.<sup>147-151</sup> In this two-part study, 624 patients with acute ischemic stroke were randomly assigned to receive alteplase or placebo within 3 hours of symptom onset.<sup>149</sup> The dose of alteplase

was 0.9 mg/kg (up to a maximum of 90 mg), with 10% of the dose administered as a bolus over 1 minute and the remainder administered as a continuous infusion over 1 hour. Approximately 50% of the patients in this study received treatment within 90 minutes.

Patients in the alteplase group were significantly more likely to have a favorable outcome at 3 months compared with those in the placebo group (absolute difference of 11–13%). The benefits of alteplase were observed for all ischemic stroke subtypes and patient subgroups, and persisted for up to 1 year.<sup>147,152</sup> Although the rate of symptomatic intracranial hemorrhage within 36 hours after the onset of stroke was significantly higher with alteplase (6.4%) compared with placebo (0.6%), no significant difference in mortality rate was noted.<sup>149</sup> Subsequent data analysis revealed that the beneficial effect of alteplase is time dependent, even within the first 3 hours of onset.<sup>153</sup> Whereas patients treated within the 90-minute and 91–180-minute time windows both derived significant benefit from alteplase, earlier therapy correlated with more favorable outcomes at 3 months.

Although the other three randomized trials involving alteplase are similar to the NINDS in study design and end points, the primary difference is the time frame within which alteplase was administered. In both the European Cooperative Acute Stroke Study (ECASS) and ECASS II, alteplase was administered within 0–6 hours of symptom onset, whereas a 3–5-hour treatment window was used in the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial.<sup>148,150,151</sup> The dose of alteplase used in the ECASS trial (1.1 mg/kg) was higher than that in the NINDS study.<sup>148</sup> Based on the findings of these trials, administration of alteplase more than 3 hours after the onset of stroke symptoms is not recommended.<sup>154,155</sup> Additional data are needed to determine whether specific patients may derive benefit from alteplase therapy during the 3–6-hour treatment window.

Patients considered eligible for thrombolytic therapy include those with a diagnosis of ischemic stroke that is causing a measurable neurologic deficit who have an onset of symptoms less than 3 hours before initiation of treatment. However, an extensive number of exclusion criteria preclude the use of thrombolytic therapy; these criteria were outlined in the preceding section. The dose of alteplase to

be administered is the same as that which was administered in the NINDS trial. During and after administration of alteplase, the patient's blood pressure should be maintained below 180/105 mm Hg to minimize the occurrence of thrombolysis-related hemorrhagic complications. In addition, the use of antiplatelet or anticoagulant agents should be withheld for 24 hours after administration of alteplase.

### Toxicology: Agents for Reversal

Although the list of antidotes for drug-induced emergencies is quite extensive, this section discusses those that are the most frequently used.

#### Glucagon

Glucagon is the drug of choice for reversing cardiovascular depression resulting from  $\beta$ -blocker toxicity, with beneficial effects in patients with calcium channel blocker overdose who are unresponsive to calcium administration.<sup>156, 157</sup> Glucagon exerts positive inotropic and chronotropic effects that are mediated by adenylyl cyclase,<sup>158</sup> which is activated by a mechanism that is independent of  $\beta$ -receptors, resulting in an increase in cyclic adenosine 3',5'-monophosphate and an increase in the influx of calcium through the L-type calcium channels.<sup>159</sup> Although no prospective clinical trials have evaluated the efficacy of glucagon in  $\beta$ -blocker or calcium channel blocker overdoses, data from multiple case reports suggest that glucagon improves heart rate, cardiac output, and blood pressure.<sup>160-164</sup> The most appropriate dosing regimen of glucagon in this setting is not well established; however, an initial bolus dose of 5–10 mg infused over 1–2 minutes is generally recommended.<sup>165</sup> The hemodynamic effects of glucagon peak within 5–10 minutes of administration of the intravenous bolus dose and last for approximately 30 minutes.<sup>166</sup> Because of its relatively short duration of action, a continuous infusion of 2–10 mg/hour should be started after the bolus dose is administered.<sup>165</sup>

At these doses, glucagon frequently causes nausea and vomiting, which can be managed with antiemetic drugs. Also, glucagon has been associated with hyperglycemia and hypokalemia; the hypokalemia likely results from the increase in plasma insulin concentration that occurs in response to the glucagon-induced hyperglycemia, which subsequently shifts the potassium intracellularly. Because of the risk of thrombophlebitis, glucagon should be reconstituted with

sterile water to a concentration of 1 mg/ml if a dose greater than 2 mg is to be administered.<sup>167</sup>

#### Calcium

Administration of calcium may improve conduction disturbances, cardiac output, and blood pressure in patients with calcium channel blocker or  $\beta$ -blocker overdose at presentation.<sup>168-171</sup> Articles describing the efficacy of calcium in the setting of calcium channel blocker overdose have reported a variable response.<sup>168, 169</sup> Although the administration of calcium has been associated with benefit in several cases of  $\beta$ -blocker overdose, its use is usually reserved for those patients who do not respond to glucagon therapy.<sup>165, 170, 171</sup>

The most appropriate dose of calcium has not been established; however, an initial intravenous bolus of 1–2 g of 10% calcium chloride or 3–6 g of 10% calcium gluconate administered over 5 minutes is generally recommended.<sup>165</sup> The dose can be repeated every 10–20 minutes for an additional 3–4 doses. Continuous infusions of calcium may be necessary to sustain hemodynamic effects in cases of severe overdose. The recommended infusion rates for calcium chloride and calcium gluconate are 0.2–0.4 and 0.6–1.2 ml/kg/hour, respectively.<sup>165</sup> The patient's heart rate, blood pressure, and serum calcium concentrations should be measured during the calcium infusion. Serum calcium concentrations can be measured 30 minutes after starting the infusion and every 2 hours thereafter throughout the duration of the infusion.<sup>172</sup>

#### Catecholamines

In cases of  $\beta$ -blocker or calcium channel blocker overdose, multiple catecholamine infusions are often required for hemodynamic support. In  $\beta$ -blocker overdoses, higher than normal doses of  $\beta$ -agonists are often needed to displace the  $\beta$ -blocker from the receptor. In this situation, while it may seem intuitive that only pure  $\beta$ -agonists such as isoproterenol or dobutamine should be effective, catecholamines with mixed  $\alpha$ -agonist properties (dopamine, epinephrine, and norepinephrine) have also been used successfully to provide hemodynamic support.

Isoproterenol appears to be effective for reversal of the associated bradycardia and conduction abnormalities in patients with  $\beta$ -blocker overdose.<sup>173</sup> However, isoproterenol may not be effective for increasing blood pressure, since the  $\beta_2$ -agonist properties can result in

vasodilation and may exacerbate hypotension. The infusion can be started at 0.5 µg/minute and then titrated to response (doses up to 800 µg/min may be required).<sup>173</sup> Dobutamine is another relatively pure β-agonist (with minimal α<sub>1</sub>-agonist activity) that has been used for the management of β-blocker overdoses. However, experience with dobutamine in this setting has been relatively limited compared with that associated with isoproterenol.<sup>162</sup> Dobutamine infusions can be started at 2.5 µg/kg/minute and titrated according to response (doses up to 30 µg/kg/min may be needed).<sup>173</sup> The administration of a mixed α-β-agonist, such as dopamine, epinephrine, or norepinephrine, is particularly useful for patients with refractory hypotension. Since existing data have not demonstrated superiority of any of the catecholamines in patients with β-blocker or calcium channel blocker overdoses, selection of a specific agent should be guided by the patient's overall hemodynamic status.

#### Digoxin Immune Antibody Fragments

The administration of digoxin-specific immune antibody fragments has been shown to be effective for the treatment of digoxin toxicity.<sup>174-176</sup> Digoxin immune antibody fragments are indicated for the treatment of life-threatening digoxin toxicity, which is defined as follows: acute ingestion of more than 10 mg in adults or more than 4 mg in children; chronic ingestions associated with steady-state serum digoxin concentrations greater than 6 ng/ml in adults or greater than 4 ng/ml in children; development of ventricular arrhythmias, progressive bradycardia, or second- or third-degree atrioventricular block (not responsive to atropine); or presence of hyperkalemia (serum potassium concentration > 5 mEq/L in adults or > 6 mEq/L in children). The dose of digoxin immune antibody fragments is expressed in terms of number of vials and can be determined from the following equation: no. of vials = total digitalis body load (mg)/0.5 mg of digitalis bound per vial. However, this equation is only of value when the amount of digoxin ingested or the serum digoxin concentration is known. If this information is not known, the dose is determined empirically; patients with acute ingestions should receive 20 vials, whereas patients with chronic toxicity (or infants and children weighing < 20 kg) should receive 6 vials. Each vial of digoxin immune antibody fragments contains 40 mg and will bind to approximately

0.5 mg of digoxin.

Serum potassium concentrations should be closely monitored after administration of the antibody fragments, as hypokalemia may develop. In addition, serum digoxin concentrations may increase substantially, since total (i.e., digoxin bound to immune antibody fragments) concentrations are being measured, rather than only unbound digoxin in the serum. Therefore, serum digoxin concentrations obtained after administration of the digoxin immune antibody fragments do not accurately represent the patient's digoxin body stores and should not be used to make subsequent treatment decisions. Serum digoxin concentrations may not become accurate until the digoxin immune antibody fragments are eliminated from the body (half-life 15–20 hrs, longer in patients with kidney disease). In the setting of kidney disease, these complexes may disassociate over time, necessitating repeated doses of the digoxin immune antibody fragments if arrhythmias recur. Therefore, determination of unbound serum digoxin concentrations should be considered for monitoring.<sup>177</sup>

#### Therapeutic Hypothermia

Anoxic brain injury as a result of cardiac arrest is a major cause of morbidity and mortality. The application of mild-to-moderate hypothermia during the post-cardiac arrest period has shown promise in improving neurologic recovery and reducing the mortality rate.<sup>12, 178</sup> The Hypothermia After Cardiac Arrest (HACA) study group conducted a multicenter trial in which outcomes were assessed after cardiac arrest.<sup>179</sup> Patients were randomly assigned either to undergo hypothermia (temperature 32–34°C) for 24 hours or to maintenance of normothermia. The primary end point was a favorable neurologic outcome at 6 months. Favorable neurologic outcomes were reported in 75 (55%) of 136 patients who were rendered hypothermic compared with 54 (39%) of 137 patients in the normothermia group (risk ratio 1.40, 95% confidence interval 1.08–1.81). In another assessment, 77 patients with cardiac arrest were randomly assigned to hypothermia (body temperature reduced to 33°C induced within 2 hrs of ROSC and continued for 12 hrs) or normothermia.<sup>180</sup> The primary outcome was survival to hospital discharge with good neurologic function. The frequency of the primary end point was 49% (21 out of 43

patients) in the hypothermia group and 26% (9 out of 34) in the normothermia group ( $p=0.046$ ). These results suggest that moderate hypothermia in patients with cardiac arrest may improve survival to hospital discharge with intact neurologic function.

Various methods have been used to induce hypothermia, including ice packs applied to armpits, neck, torso, and groin; covering the patient with a cooling blanket (covered with a sheet); and infusing cold saline (1–2 L of 4°C normal saline) through peripheral or femoral vein access.<sup>180–182</sup> The use of the jugular or subclavian vein for cold saline infusion should be avoided. Current guidelines recommend a goal temperature of 32–34°C, to be maintained for 12–24 hours. Therapeutic hypothermia is assigned a class IIa indication for patients with ventricular fibrillation and a class IIb indication in patients with non-ventricular fibrillation arrest occurring in or out of the hospital.<sup>5</sup>

Patients undergoing hypothermia should undergo sedation with use of a continuous benzodiazepine infusion (midazolam or lorazepam) and a continuous fentanyl infusion at a rate of 25–100 µg/hour. In addition, if shivering occurs during hypothermia, then additional therapy with a neuromuscular blocking agent should be considered.<sup>179, 182</sup> Although therapeutic hypothermia appears to be associated with benefit, larger studies are needed to determine the optimum treatment method, goal temperature, and duration of therapy.

### Key Elements in Drug Administration

Appropriate CPR resulting in good femoral pulses may provide only 25–30% of normal cardiac output; therefore, distribution of administered drugs to the appropriate site of action may be suboptimal.<sup>38, 183, 184</sup> Consequently, the administration of normal saline 10–20 ml after drug administration, with continued CPR, is recommended in the 2005 guidelines to facilitate drug distribution.<sup>5, 8</sup> Chest compressions should not be interrupted for drug administration. The time of maximum pharmacologic effect may depend on the distance from the heart (peripheral vs central) at which the specific drug is administered and the effectiveness of the CPR. If a peripheral infusion site is used, a normal saline flush of 20 ml should follow drug administration.<sup>5</sup> If the arm is used, it should be elevated. The closer upstream to the heart that a drug is administered, the higher the peak

concentration and the more rapid the onset of desired response.<sup>185–188</sup>

Drug therapy must be carefully coordinated with other adjunctive therapy. The 2005 guidelines stress the importance of having any necessary unit-dose preparation of currently recommended doses of drugs (which are frequently not provided in manufactured prefilled syringes) available in advance to avoid unnecessary treatment delays.<sup>5</sup> Any drug preparation should be labeled appropriately with the name and dose of the drug. The advanced preparation of generic preprinted labels with the drug and a space in which the quantity can be rapidly written can expedite this process. Preprinted labels for intravenous drugs administered by continuous infusions describing the amount to add to a prespecified volume and the common infusion rates can also simplify the process and reduce the risk of errors.

When attempting to clear air bubbles from the line, a few bubbles (approximately 5 ml) should pose no significant concerns, as this volume is frequently administered intravenously in bubble tests used to detect presence of a patent foramen ovale. Verify that the infusion is reaching the patient by checking for drips in the drip chamber (i.e., the stopcock is not in the “off” position), and that the drug is infusing into the patient and not onto the bedside or floor. The 2005 guidelines note that if intravenous access is not available, then intraosseous administration should be considered.<sup>5</sup> The time for a drug to reach the heart after intraosseous injection is approximately 2 minutes.

If intraosseous administration is not an option, then intubation followed by the administration of an agent approved for endotracheal use should be performed.<sup>8</sup> After drug administration by the endotracheal tube route, approximately 1–2 minutes are required for peak concentrations to occur in the heart.<sup>186</sup> Drugs administered through an endotracheal tube should be diluted in 5–10 ml of fluid to allow adequate delivery; peak cardiac concentrations may be lower than those that occur after intravenous or intraosseous administration.<sup>186</sup> Dilution with sterile water instead of saline may improve the absorption of agents such as lidocaine or epinephrine.<sup>189–191</sup> Although the doses of drugs delivered through an endotracheal tube are recommended to be 2–2.5 times the intravenous dose, one analysis suggests that these doses may be too low and that higher endotracheal doses of atropine or epinephrine should be evaluated.<sup>192, 193</sup>

Simplified teaching tools such as “one dose is equivalent to one ampule” or the drug-shock-drug-shock pattern should be avoided, as these might lead to either under- or overdosing or to delays in repeating administration of an agent such as epinephrine within the desirable time period.<sup>194</sup> In some cases, rapid delivery of a drug may require some flexibility in the dose or the volume in which it is prepared in, but these should be kept as minimal as possible.

### Role of the Pharmacist

In the 1960s and early 1970s, pharmacists began expanding their role beyond traditional drug distribution functions to more clinical roles including participation on the cardiac arrest team. Roles included drug distribution, provision of supportive information, recording of drug administration, and restocking of necessary supplies.<sup>195</sup> The multiple recommended treatment options combined with the complexity of the drug therapy, including a broader amount of clinical data and variety of intervention approaches in the hospital setting, have created the need for an active role for pharmacists in cardiac arrest cases. More recently, roles of the pharmacist on cardiac arrest teams have continued to include calculation of drug doses, provision of drug information, preparation of drugs in advance of request for administration, and documentation of activities and interventions during the cardiac arrest.<sup>196</sup> Additional roles of the pharmacist at some institutions include infusion pump preparation, drug administration, and performance of chest compressions and artificial respiration.<sup>197</sup>

Survey data indicate that approximately 32–37% of institutions include pharmacists as a member of the cardiac arrest team.<sup>196–199</sup> Determination of reasons for not including pharmacists as a member of the cardiac arrest team and identification of barriers inhibiting pharmacists' participation should be considered a priority. Training modules to prepare pharmacists for participation in cardiac arrest cases appear to be limited, and many do not include American Heart Association–approved ACLS training, which should be a minimum requirement for pharmacists and others to participate in cardiac arrest management. In some institutions, personnel limitations, specific systems of delivering pharmaceutical care, and/or the lack of around-the-clock pharmacy services create additional challenges. Training pharmacists to

understanding the entire cardiac arrest management process, including the location of drugs on the “crash cart,” preparation of drugs, understanding the rationale for specific drug therapy for the management of each type of cardiac arrest, and a clear understanding of the role of the pharmacist and other team members is necessary to facilitate pharmacist participation as integral members of the cardiac arrest team. Pharmacists can also participate in educating clinical personnel involved in managing cardiac emergencies regarding approaches to the use of pharmacologic adjuncts.

In situations where a pharmacist is not available 24 hours, having them attend cardiac emergencies when available can provide an opportunity to observe how the drugs are used, identify areas for improvement, and facilitate means to implement a change. Some drugs may not be readily available, and the pharmacist could be a source of quick access to those agents.<sup>200</sup> Additional activities may include an assessment of the patient's drug profile and recent laboratory values, and notifying the team leader of those observations and any follow-up suggestions. During the postresuscitative period, the pharmacist could participate in prompt initiation of the postresuscitation management plan.

### Conclusion

Pharmacotherapy for the management of cardiac arrest is complex and varied, depending on the specific nature and cause of the life-threatening event. We attempted to provide pharmacists with a review of the rationale for specific pharmacotherapy decisions for management of cardiac arrest, and to provide an update regarding the most recent guidelines for management of cardiac arrest. Pharmacists may play a vital role as members of the cardiac arrest team, provided appropriate education and training have occurred.

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