

# Use of Pressors in the Treatment of Cardiac Arrest

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## Topic 1: Use of Epinephrine in Adults

### 1992 GUIDELINES

The 1992 guidelines recommend epinephrine (1 mg IV) as the first pressor agent in cardiac arrest. A higher dose of epinephrine (5 mg or  $\approx 0.1$  mg/kg) was considered acceptable if the 1-mg dose failed (Class IIb), but the use of a higher dose was neither recommended nor discouraged. (*JAMA*. 1992;268:2208.)

### PROPOSED ADDITION OR CHANGE

Evidence does not support the use of high-dose epinephrine therapy (HDE) for pulseless cardiac arrest. HDE does not improve the rate of survival and may be associated with an increase in neurologic complications (Class III).

### NEW SCIENCE

Since 1992, animal and human studies have demonstrated both beneficial and toxic physiologic effects of HDE during CPR.<sup>1-12</sup> Initial or escalating HDE sometimes improves initial rhythm, return of spontaneous circulation (ROSC), and early survival, but it does not improve long-term survival or neurologic outcome. Eight prospective, randomized, clinical studies of good to excellent quality (level of evidence [LOE] 2)<sup>13-20</sup> compared initial HDE with standard-dose epinephrine therapy (SDE) in more than 7,000 adult victims of cardiac arrest and demonstrated consistently equivalent survival to

hospital discharge and dismal neurologic outcome with both therapies, even in subgroups of patients with refractory ventricular fibrillation (VF) and in-hospital arrest. The panel extensively discussed 1 large study, reported only in abstract form, of 2,920 victims of out-of-hospital arrest.<sup>21</sup> An overall summary of 9,462 patients randomly assigned to receive HDE or SDE showed that early ROSC and survival to hospital admission are improved significantly with use of HDE (26.1% with HDE versus 23.4% with SDE,  $P < .01$ ) but that survival to discharge (2.9% with HDE versus 3.0% with SDE,  $P = .73$ ) and neurologically intact survival (2.2% with HDE versus 2.3% with SDE,  $P = .75$ ) are not improved. HDE has not been consistently harmful. These studies mostly addressed the initial and cumulative dose of epinephrine and not the use of an escalating-dose strategy after failure of the standard 1-mg dose. A study<sup>17</sup> of 140 patients (LOE 2) randomly assigned to receive HDE ( $n = 78$ ) or SDE ( $n = 62$ ) for VF or asystole refractory to advanced cardiac life support (ACLS) did not show significant differences in hemodynamic response or return of neurologic function, and no patient survived to hospital discharge. An additional excellent in-hospital study (LOE 2)<sup>20</sup> of 40 ICU patients with sepsis-associated cardiac arrest did not show beneficial or toxic hemodynamic effects as a result of the use of SDE or HDE. Results of a fair-quality (LOE 3) study (randomization was suboptimal) involving 194 victims of in-hospital or out-of-hospital cardiac arrest suggested a beneficial change in rhythm with HDE compared with SDE or placebo, but there were no significant differences in survival among groups.<sup>22</sup> A larger, fairly good (LOE 4) out-of-hospital study involving historical control subjects (SDE,  $n = 594$ ; HDE,  $n = 580$ ) also failed to demonstrate any clinically important difference in outcome or toxicity between the 2 groups.<sup>23</sup> A good-quality retrospective study (LOE 4) evaluated neurologic outcome by cerebral performance category up to 6 months after resuscitation from VF-induced cardiac arrest and suggested that a high cumulative dose of epinephrine is associated with worse neurologic outcome than are more standard doses.<sup>24</sup> In this study of 151 patients in whom ROSC occurred more than 3 minutes after initial electrical shocks, 88 patients survived with poor neurologic function and 63 survived with good neurologic function. Not surprisingly, 77 of the 88 patients who had poor neurologic function died within 6 months of the arrest, as did 3 of the 63 patients who had good initial neurologic function. The cumulative epinephrine dose was higher in the group with poor neurologic function than in the group with good neurologic function (mean dose, 4 versus 1 mg, respectively;  $P < .001$ ). Initial

ROSC (84%) was higher than in other studies. As expected, poor neurologic function correlated with a longer duration of untreated cardiac arrest (no flow) and cardiopulmonary resuscitation (CPR) (low flow). But even after controlling for duration of arrest and confounding factors, a higher epinephrine dose was associated with worse neurologic outcome. Another prospective clinical trial involving 49 victims of witnessed cardiac arrest also seems to corroborate the conclusion that poor prognosis and adverse hemodynamic effects are associated with use of high cumulative doses of epinephrine.<sup>12</sup>

One additional clinical study<sup>27</sup> reviewed by panelists after the Evidence Evaluation Conference compared SDE (1 mg) with HDE (5 mg). Doses were repeated every 5 minutes. No significant differences in ROSC, survival, or neurologic outcome were observed, although ROSC tended to occur more frequently in patients who received SDE. The population studied had a high prevalence of coronary artery disease and myocardial ischemia.

Laboratory studies have shown both beneficial and harmful physiologic effects and outcomes resulting from the use of HDE. Twenty-four-hour survival studies in animals also have shown no benefit of HDE compared with SDE in VF-<sup>1</sup> and asphyxia-induced<sup>2</sup> arrest. In addition, HDE can lead to a postresuscitation toxic hyperadrenergic state with arrhythmias, increased intrapulmonary shunting, and increased mortality.<sup>1,2,5,7,10</sup> Epinephrine has also been shown to worsen postresuscitation cardiac dysfunction in animals,<sup>8</sup> and a higher epinephrine cumulative dose worsens postresuscitation cardiac dysfunction in humans.<sup>12</sup> Evidence from other human studies (LOE 4) suggests that, despite very high prevailing plasma epinephrine concentrations during cardiac arrest, further increases in epinephrine elicit potentially beneficial biologic effects in certain patients.<sup>11,25</sup> Although SDE is currently considered the standard of care, no randomized, prospective study has shown that SDE increases long-term survival in cardiac arrest compared with repeated electrical countershocks, CPR, and other standard ACLS therapies.

## EVALUATION AND DEBATE

Routine use of initial and repeated doses of epinephrine has not definitively improved survival outcome in adult victims of cardiac arrest. Adrenergic therapy is indicated during CPR to increase coronary and cerebral perfusion pressures, thus improving the likelihood of ROSC. For the 1992 guidelines, the background rationale for the recommended dosage of epinephrine, use of adrenergic

agents in place of epinephrine,<sup>26</sup> and the potential use of surrogate end points were reviewed. Data from 3 large prospective, blinded, unpublished clinical trials of 2,415 patients comparing initial SDE and HDE were reviewed. Since 1992, 9 good-to-excellent prospective, randomized, clinical studies (LOE 2) have compared initial SDE and HDE in adults and consistently demonstrated no improvement in survival to hospital discharge or neurologic outcome with HDE, even in subgroups of patients with refractory VF and in-hospital arrest. HDE has not been consistently harmful, particularly for survival to discharge and neurologically intact survival. These studies mostly addressed initial and cumulative doses, not the currently recommended escalating doses after failure of the 1-mg dose. It was noted that survival and survival with intact neurologic functioning was less than 3% overall. Panelists discussed and speculated on the potential for underestimating adverse effects because overall outcome was so dismal. The potential to miss important subgroups in which HDE might be beneficial was identified (eg, survival when time to epinephrine administration was < 10 minutes increased from 11% to 23% with HDE in 1 study<sup>13</sup>). Panelists thought HDE might be applied selectively to patients who are beyond a reasonable expectation of beneficial response. Furthermore, it was thought that the risk of applying new or innovative therapies might be minimal when overall outcome is so poor.

Intense systemic vasoconstriction may be critically important for coronary perfusion during early CPR and resuscitation, but persistence of the effects of intense vasoconstriction during postresuscitation myocardial ischemia and dysfunction may be deleterious. Adrenergic stimulation may be beneficial or detrimental depending on the patient. Large interpatient variability in catecholamine response is well established in both the nonarrest and arrest settings. Higher doses of epinephrine may have direct toxic effects on the brain. A dose that is dangerous in 1 person may be lifesaving in another. Individual titration of the epinephrine dose to bring about the desired effect seems most reasonable whenever possible. Increased attention to postresuscitation pressor support after ROSC was identified as a potentially productive area for future investigation.

Panelists discussed whether initial or rescue HDE might result in return of cardiac function with irreversible brain injury. Selection of an appropriate critical outcome dictates the Emergency Cardiac Care Committee's decisions regarding the recommended dosage of epinephrine. The panel discussed appropriate surrogate outcomes, including beneficial rhythm change, hemodynamics, ROSC,

survival to admission, survival to discharge, intact neurologic survival, economic efficacy, patient satisfaction, and quality of life. If increased coronary perfusion pressure, increased ROSC, or increased short-term survival is selected as the critical outcome, a Class IIa rating might be assigned to HDE. If postresuscitation myocardial dysfunction or hospital cost is selected as the critical outcome, a Class III rating might be assigned to HDE. If survival to discharge or intact neurologic survival is selected as the gold standard critical outcome, a Class Indeterminate rating is most appropriate. Panelists acknowledged the need to honestly acknowledge the LOE for specific outcomes and to differentiate the process of evidence evaluation from that of algorithm (teaching tool) development. Improved ROSC and survival to hospital admission without a concomitant increase in survival to discharge, neurologically intact survival, or improved quality of life might advance the science of resuscitation or improve organ recovery and donation, but those outcomes may not be beneficial or cost-effective for the individual or society. Retrospective studies suggest that a high cumulative epinephrine dose is associated with worse hemodynamic and neurologic outcomes, even when the duration of cardiac arrest (no flow) and interval of CPR (low flow) are taken into account. This does not, however, prove a causal effect. A synthesis of accumulated knowledge from preclinical and clinical cardiac arrest studies suggests that an isolated change in the dose of pressor administered at the time of arrest is unlikely to demonstrate statistically significant effects on long-term outcome.

There is increasing evidence that routine administration of higher-than-standard dosages of epinephrine does not consistently improve survival or neurologic outcome among a broad spectrum of cardiac arrest patients. After constructive debate, it was acknowledged that the lack of high-level data demonstrating significant differences in survival outcome between HDE and SDE suggests that the guidelines recommendations should not be dramatically different for HDE and SDE. Populations with increased risk and those most likely to benefit (eg, patients with catecholamine-refractory conditions) need to be identified, and recommendations should neither preclude nor encourage the use of higher dosages of epinephrine at this time.

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#### PROPOSED GUIDELINES

A high initial intravascular dose of epinephrine in victims of cardiac arrest may increase coronary perfusion pressure and ROSC but may also exacerbate postresuscitation

myocardial dysfunction. HDE does not improve long-term survival and neurologic outcome or definitively cause harm. Therefore, routine use of HDE is not recommended. There is conflicting evidence for and against the use of higher dosages of epinephrine in cardiac arrest when a 1-mg dose has failed (Class Indeterminate).

## Topic 2: Use of Epinephrine in Infants and Children

### 1992 GUIDELINES

The 1992 guidelines recommended second and subsequent epinephrine doses of 0.1 mg/kg for unresponsive pediatric patients with asystolic and pulseless cardiac arrest (Class IIa) (*JAMA*. 1992;268:2268). An epinephrine dose of 0.01 to 0.03 mg/kg was recommended for newborns with asystole or a spontaneous heart rate of less than 80 beats/min, despite adequate ventilation with 100% oxygen and chest compression (Class I), repeated every 3 to 5 minutes. The guidelines note that some children and adults who do not respond to standard dosages of epinephrine will respond to doses as high as 0.2 mg/kg, but the available data are inadequate to evaluate the efficacy and safety of higher dosages of epinephrine in newborns. (*JAMA*. 1992;268:2279.)

### PROPOSED ADDITION OR CHANGE

Evidence supports the current recommendations for an initial dose of epinephrine of 0.01 mg/kg for pulseless cardiac arrest in infants and children. Higher second and subsequent dosages of epinephrine are acceptable and useful for infants and children (Class IIb), although HDE does not appear to improve survival. HDE is potentially harmful for neonates (Class III).

### NEW SCIENCE

Since 1992, both physiologic benefits and toxic effects of HDE during CPR have been demonstrated in relevant adult and pediatric animal and human studies.<sup>1-14</sup> (See also "Additional Resources": Horowitz 1996 and Berkowitz 1991.) Evidence from human studies (LOE 4) suggests that, despite very high prevailing plasma epinephrine concentrations during cardiac arrest, further increases in epinephrine elicit potentially beneficial biologic effects in certain patients.<sup>11,16</sup> An excellent study<sup>22</sup> (LOE 2) of 40

adult ICU patients with sepsis-associated cardiac arrest did not show beneficial or toxic hemodynamic responses to either SDE or HDE. Two excellent pediatric animal studies (LOE 6), of VF<sup>-1</sup> and asphyxia-induced arrest,<sup>2</sup> compared HDE with SDE; the results suggest that HDE may induce a hyperadrenergic state and may be associated with impaired early hemodynamics, worse survival, and worse neurologic outcome. Optimal chest compressions and early advanced life support were provided in addition to epinephrine, resulting in trends toward improved early ROSC and increased morbidity and mortality in the early postresuscitation phase in animals given HDE but no differences in long-term or intact neurologic survival.

Good- to excellent-quality randomized studies<sup>15-24</sup> (LOE 2) evaluating more than 9,000 adults showed that early ROSC and survival to hospital admission are improved statistically with use of HDE (26.1% with HDE versus 23.4% with SDE,  $P < .01$ ) but that survival to discharge (2.9% with HDE versus 3.0% with SDE,  $P = .73$ ) and neurologically intact survival (2.2% with HDE versus 2.3% with SDE,  $P = .75$ ) are not improved, even in subgroups of patients with refractory VF and in-hospital arrest. Nevertheless, the lack of improvement in survival to discharge and neurologically intact survival is not definitive evidence of harm. These studies mostly addressed initial and cumulative dosages in adults, not rescue dosing after failed SDE. Four fair-quality retrospective studies of HDE in pediatric cardiac arrest (total,  $n = 213$ ; out-of-hospital,  $n = 162$ ; in-hospital,  $n = 51$ ) did not show ROSC or survival benefits. These retrospective studies revealed no clear clinical benefit of routine use of high or escalating dosages of epinephrine in either out-of-hospital (see "Additional Resources": Dieckmann, *Pediatrics*. 1995; Ronco, *Arch Pediatr Adolesc Med*. 1995; Kuisma, *Resuscitation*. 1995) or in-hospital ("Additional Resources": Carpenter, *Pediatrics*. 1997) settings. For example, 1 study of 65 pediatric patients with nontraumatic out-of-hospital arrest ("Additional Resources": Dieckmann, *Pediatrics*. 1995) had long, undocumented arrest intervals, and 55% to 69% of patients were victims of sudden infant death syndrome; electrical defibrillation was attempted before administration of epinephrine or endotracheal intubation in 47% of patients with asystole. HDE was delivered by a combination of endotracheal and intravascular routes; some were given initial HDE, and some were given rescue HDE. Overall survival was poor (3%), and there were no neurologically intact survivors. A review of 51 pediatric inpatients ("Additional Resources": Carpenter, *Pediatrics*. 1997) suggested a trend toward

worse ROSC and 24-hour survival outcomes with HDE, but there were no differences in survival to discharge or neurologically intact survival between those given HDE and those given SDE. Again, HDE was delivered by a combination of endotracheal and intravascular routes. More SDE patients were in ICU before arrest, and a "high dose" was defined as any dose greater than 0.03 mg/kg regardless of administration route. One preliminary report<sup>28</sup> of a randomized, blinded comparison of SDE and HDE for out-of-hospital pediatric cardiopulmonary arrest (LOE 2) was mentioned, but this study has not undergone peer review and was therefore not discussed in detail. A collective review of pediatric cardiac arrest outcomes from 44 studies conducted over 27 years (n = 3,094) did not show HDE as an independent factor for successful resuscitation outcomes of ROSC, short- or long-term survival, or neurologically intact survival.<sup>29</sup> Only 30% of arrests were witnessed, and only 30% of victims received bystander CPR. The study was not designed to specifically evaluate the effect of epinephrine dose. A longer duration of resuscitation and a greater number of epinephrine doses have been consistently associated with poor survival outcome.<sup>29-32</sup> A higher cumulative epinephrine dose has also been correlated with adverse hemodynamic effects and poor neurologic outcome in several adult human studies, even after controlling for duration of arrest and confounding factors.<sup>12,24</sup>

Although the current standard of care is to administer epinephrine in standard and higher-than-standard dosages repeatedly during resuscitation, no randomized, prospective study of SDE, HDE, or any epinephrine dosing sequence in pediatric or neonatal cardiac arrest has been reported in the peer-reviewed literature.

## EVALUATION AND DEBATE

Recommendations for initial doses of HDE for infants and children must be extrapolated from adult studies and recommendations because this therapy has not been studied in pediatric populations. Routine use of initial and repeated dosages of epinephrine has not definitively improved survival in adult victims of cardiac arrest. Background and rationale supporting the 1992 pediatric epinephrine recommendations were reviewed.<sup>26,33</sup> ("Additional Resources": Zaritsky, *Ann Emerg Med.* 1993.) In 1997 and 1999, the International Liaison Committee on Resuscitation published advisory statements reinforcing consensus practice guidelines, including the 1992 epinephrine dosage recommendations, but those statements also highlighted special concern for patients with a

high risk of intracranial hemorrhage and the disappointing efficacy and potentially detrimental effects of HDE.<sup>34,35</sup> Prior pediatric recommendations for higher rescue dosages of epinephrine after failure of SDE were based on the results of 1 fair-quality case series (n = 20) of rescue HDE for witnessed arrest with excellent early advanced life support, an average time to CPR of 3.4 minutes, and an average time to administration of epinephrine of 4.8 minutes.<sup>33</sup> Three of 20 survivors were premature infants and received intra-arterial epinephrine. Dismal overall outcome has been reported for pediatric patients with refractory arrest requiring multiple doses of SDE.

Findings of several excellent, relevant HDE animal studies published since 1992 accurately reflect the human experience: Early adrenergic therapy combined with effective assisted circulation (chest compressions) increases coronary and cerebral perfusion pressures and improves the likelihood of ROSC and short-term survival. The effects of intense adrenergic vasoconstriction, however, are associated with worse post-ROSC hemodynamics and toxicity and long-term survival and neurologic outcomes equivalent to that seen with SDE. Adrenergic stimulation may be beneficial or detrimental depending on the patient. Great interpatient variability in catecholamine response is well established in both nonarrest and arrest settings, particularly in infants and children, in whom three to fivefold differences in catecholamine clearance are common. An adrenergic dose that is dangerous in 1 person may be lifesaving in another. Individual titration of the epinephrine dose to bring about the desired physiologic effects seems appropriate. Post-resuscitation vasopressor support after ROSC was identified as a potentially productive area for future investigation.

Physiologic benefits of epinephrine and  $\alpha$ -adrenergic administration during CPR have been demonstrated in animals and humans and provide the physiologic basis for advocating the use of HDE in refractory cardiac arrest and prolonged pediatric resuscitation. Nevertheless, 24-hour survival and neurologic outcome have not been improved by the use of HDE in relevant animal models. The  $\beta$ -adrenergic stimulation and postresuscitation vasoconstrictive effects of epinephrine would be expected to be relatively well tolerated in young and healthy hearts. Data extrapolated from prospective, randomized studies comparing initial HDE with SDE in more than 9,000 adults in a variety of settings demonstrate trends toward early improved ROSC but no improvement in overall survival or neurologic outcome. These studies tested initial HDE, not rescue therapy specifically. The 4 fair-quality

retrospective studies of HDE in pediatric cardiac arrest did not show ROSC or survival benefits. Methodologic concerns about mixing of high and standard dosages, routes of administration, lack of prospective data, and patient selection preclude definitive conclusions. The dosage of epinephrine cannot be adequately evaluated independently unless it is given relatively early to patients who appear to have good potential for successful resuscitation and unless it is coupled with excellent advanced life support and postresuscitation care. HDE may have been applied selectively to patients in whom there was no reasonable expectation of a beneficial response. Good-quality retrospective, clinical pediatric reviews revealed no survival benefit of the use of high or escalating dosages of epinephrine and associate both a higher cumulative dose and a longer duration of resuscitation with poor outcome. Retrospective pediatric and adult studies suggest that a higher cumulative epinephrine dosage may be associated with worse neurologic outcome even when duration of untreated cardiac arrest (no flow) and interval of CPR (low flow) are taken into account. The association of higher epinephrine dosages with worse neurologic outcome does not prove a causal effect; it may simply be a marker of more severe illness or a longer duration of unsuccessful resuscitation. A synthesis of accumulated knowledge from preclinical and clinical cardiac arrest studies suggests that an isolated change in the dose of pressor administered at the time of arrest is unlikely to result in statistically significant effects on long-term outcome.

Caveats specific to the newborn and neonatal resuscitation were discussed. Epinephrine therapy is administered infrequently to neonates (see "Additional Resources": *Finer, Pediatrics*. 1999 and *Chamnanvanakij, Resuscitation*. 2000), but no specific comparisons of SDE and HDE have been published. The newborn, particularly the premature neonate, is at particularly high risk for hypoxic, ischemic, and hemorrhagic cerebral injury (see "Additional Resources": *Horowitz, Ann Emerg Med*. 1996), which may be exacerbated by systemic hypertension and cerebral vasoconstriction.

Panelists discussed and speculated on the potential risk for masking potentially beneficial or adverse effects of epinephrine by using and studying this therapy in a group of patients with such a dismal expected survival outcome. Furthermore, the relatively low risk of applying new or innovative therapies when overall outcome is so poor was discussed. Initial or rescue HDE has the potential to result in a return of cardiac function with irreversible brain injury.

Selection of critical outcome targets is critical to the Emergency Cardiac Care Committee's guideline recommendations. The panel discussed appropriate surrogate outcomes, including beneficial rhythm changes, hemodynamic effects, ROSC, survival to admission, survival to discharge, neurologically intact survival, economic efficacy, patient satisfaction, and quality of life. If increased coronary perfusion pressure, increased ROSC, or increased short-term survival is selected as the critical outcome, a Class IIa rating might be assigned to HDE. If postresuscitation myocardial dysfunction or hospital cost is selected as the critical outcome, a Class III rating might be assigned to HDE. If survival to discharge or intact neurologic survival is selected as the gold standard critical outcome, an Indeterminate rating is most appropriate. Panelists recognized the need to acknowledge LOE for specific outcomes and to differentiate the process of evidence evaluation from that of algorithm (teaching tool) development. Improved ROSC and survival to hospital admission without a concomitant increase in survival to discharge, intact survival, or improved quality of life might advance the science of resuscitation or improve organ recovery and donation but might not be beneficial or cost-effective for the individual or society.

No prospective, randomized study of epinephrine dosing in pediatric or neonatal patients has been reported. It was acknowledged that the lack of good pediatric data on significant outcome differences between HDE and SDE, even between SDE and placebo, severely limits the ability to make evidence-based recommendations and the strength (ie, class of recommendation) of those that are made. There is increasing evidence that routine administration of higher-than-standard dosages of epinephrine does not consistently improve ROSC, survival, or neurologic outcome among a broad spectrum of pediatric victims of cardiac arrest. Populations with increased risk (eg, premature neonates with a high risk for intracranial hemorrhage or documented myocardial ischemia) and those most likely to benefit (eg, those with catecholamine-refractory conditions) need to be identified, and recommendations should neither preclude nor encourage higher dosages of epinephrine at this time.

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## PROPOSED GUIDELINES

Based on discussion and debate at the Evidence Evaluation and Guidelines 2000 Conferences, the recommended initial resuscitation dose of epinephrine for pediatric cardiac arrest is 0.01 mg/kg (0.1 mL/kg of 1:10,000 solution) given by the intravenous or intraosseous route or 0.1 mg/

kg (0.1 mL/kg of 1:1,000 solution) given by the tracheal route. Repeated doses administered every 3 to 5 minutes are recommended for ongoing arrest. The same dose of epinephrine is recommended for second and subsequent doses for unresponsive asystolic and pulseless arrest, but higher dosages of epinephrine (0.1 to 0.2 mg/kg [0.1 to 0.2 mL/kg of 1:1,000 solution]) by any intravascular route may be considered for special resuscitation circumstances (Class IIb).

### Topic 3: Use of Vasopressin

#### 1992 GUIDELINES

None.

#### PROPOSED ADDITION OR CHANGE

Evidence from small clinical trials in adults and several animal studies support the use of vasopressin, which provides benefit equivalent to that of epinephrine, for treatment of shock-refractory VF-cardiac arrest (Class IIb in adults, Class Indeterminate in non-VF-cardiac arrest and for infants and children).

#### NEW SCIENCE

Since 1992, vasopressin has been increasingly identified as an important endogenous endocrine hormone that increases during cardiac arrest and CPR; the level of vasopressin also correlates with resuscitation outcome.<sup>36-40</sup> In 60 victims of out-of-hospital cardiac arrest, concentrations of plasma vasopressin and adrenocorticotropin were significantly higher during CPR in patients with ROSC, but there was no difference in endothelin concentrations between resuscitated and nonresuscitated patients. Both before and after epinephrine administration, plasma epinephrine and norepinephrine concentrations were significantly higher in patients who died than in those who survived.<sup>41</sup> Interactions between endogenous vasopressors during CPR are complex.<sup>42,43</sup> Laboratory studies suggest that vasopressin stimulation of V<sub>1</sub> receptors causes moderately selective peripheral vasoconstriction of skin, skeletal muscle, intestine, and fat with relatively less constriction of coronary, cerebral, and renal vasculature. Vasopressin produces minimal vasodilatation in skeletal muscle and minimal increase in myocardial oxygen demand in VF or after resuscitation. Animal models of cardiac arrest and CPR confirm increased vital organ per-

fusion after administration of vasopressin compared with epinephrine under certain circumstances.<sup>37,43-56</sup> (See also "Additional Resources": Chugh, *Circulation*. 1997; Frishman, *J Clin Pharmacol*. 1998; Kelly, *Ann Pharmacother*. 1997; and Wenzel, *Dtsch Med Wochenschr*. 1998.)

Three published clinical studies provide evidence supporting the use of vasopressin. One good-quality (LOE 2) prospective, randomized study<sup>57</sup> demonstrated a short-term survival advantage, and 2 good-quality (LOE 5) studies<sup>42,58</sup> of rescue therapy compared vasopressin with epinephrine. The 3 studies describe the outcome of 38 adult victims of cardiac arrest. In a case series of 8 patients with shock-refractory arrest (6 with VF, 2 with pulseless electrical activity), patients were given 40 units of vasopressin intravenously; ROSC occurred in all 8 patients, and 3 (38%; 2 with VF, 1 with pulseless electrical activity) survived to hospital discharge.<sup>58</sup> Morris et al<sup>42</sup> administered vasopressin 1 U/kg IV to 10 patients after unsuccessful ACLS, including epinephrine administration and demonstrated an increase in coronary perfusion pressure in 4 (40%) but no ROSC. The prospective, randomized study<sup>57</sup> (LOE 2) compared 40 units of vasopressin with 1 mg of epinephrine for out-of-hospital, shock-refractory, VF-arrest in adults and showed encouraging trends in ROSC (80% versus 55%, respectively; *P*=.18), 24-hour survival (60% versus 20%, respectively; *P*=.02), and survival to hospital discharge (40% versus 15%, respectively; *P*=.16). Unpublished data from a large, prospective, randomized in-hospital study comparing 40 units of vasopressin with 1 mg of epinephrine<sup>59</sup> (*n* = 201) were reviewed and suggested no survival or neurologic outcome benefit from the routine initial use of vasopressin, but conclusions based on that data were limited by its preliminary nature. Vasopressin has been reported to exert vasopressor effects in children with vasodilatory shock and critically ill pressor-dependent children during evaluation for brain death.<sup>60,61</sup> No pediatric or neonatal human data on the safety or efficacy of vasopressin in pediatric cardiac arrest has been published.

Twenty-seven animal studies (LOE 6) provide evidence supporting the use of vasopressin; all but 2<sup>52,62</sup> modeled VF. Several excellent studies<sup>48,55,62-66</sup> (LOE 6) showed hemodynamic improvement with 0.8 U/kg of vasopressin compared with 200 μg/kg of epinephrine. In short-term<sup>64</sup> and prolonged<sup>48,55,56,62,65</sup> cardiac arrest, vasopressin significantly improved hemodynamic variables, vital organ blood flow, and cerebral oxygen delivery during CPR compared with HDE. Fair- to good-quality studies (LOE 6) show improved hemodynamics and ROSC advantage with use of vasopressin compared with

placebo<sup>49,51,64,65,67</sup> and HDE.<sup>48,62</sup> Repeated dosages of vasopressin improved coronary perfusion pressure, the rate of successful defibrillation, and 60-minute survival more than epinephrine in an adult porcine model of prolonged cardiac arrest and ACLS.<sup>44</sup> In 1 study, vasopressin impaired cephalic mesenteric blood flow during CPR and in the early postresuscitation phase, but it did not result in an antidiuretic response. Neither renal blood flow nor renal function was influenced by vasopressin or epinephrine in this investigation.<sup>53</sup> A bolus dose of vasopressin followed by a low-dose dopamine infusion improved postresuscitation blood flow to the mesenteric bed in a similar animal model of cardiac arrest.<sup>56</sup> The interaction of vasopressin and epinephrine may result in comparable myocardial blood flow but can lead to decreased cerebral perfusion in certain circumstances.<sup>52</sup> The impact on neurologic and survival outcome in models of pediatric asphyxia-induced arrest suggests that the interplay of vasopressors may be important.<sup>56</sup> A rodent study demonstrated that  $V_1$ - and  $\alpha$ -adrenergic receptors may affect the same intracellular transduction pathway,<sup>68</sup> which may contribute to the observed interaction. Vasopressors increase vital organ blood flow during CPR, but endocardial perfusion during CPR remains suboptimal,<sup>64</sup> creating a risk of myocardial ischemia. A combination of vasopressin and nitroglycerin significantly improved endocardial blood flow and the endocardial/epicardial blood flow ratio compared with vasopressin alone.<sup>69</sup> Administration of vasopressin appears to be equally effective by the endobronchial, intravenous, or intraosseous route.<sup>51,70</sup> Postresuscitation systemic vasoconstriction and myocardial depression, potential effects of vasopressin, may be concerns, but these effects are reversible.<sup>46</sup> A laboratory study of repeated pressor administration during prolonged CPR in piglets demonstrated that vasopressin dramatically improves long-term survival, intact neurologic recovery, and cerebral pathology compared with epinephrine or saline placebo.<sup>67</sup> Vasopressin has demonstrated efficacy in special resuscitation circumstances including hypothermia, anesthesia-associated arrest, hypovolemia, and vasodilatory shock.<sup>61,65,71,72</sup> Published human clinical studies have demonstrated improvement of the surrogate outcomes of hemodynamics, early ROSC, and survival to hospital admission, but no significant benefits for long-term survival or neurologic outcome have been demonstrated.<sup>59</sup>

One study comparing vasopressin with epinephrine in a swine model of asphyxia-induced cardiac arrest and CPR was reviewed; findings of this study suggest vasopressin results in worse myocardial blood flow and ROSC

than epinephrine.<sup>54</sup> The group treated with both vasopressin and epinephrine had intermediate outcomes. ROSC rates were 6 of 6 with epinephrine alone, 0 of 6 with vasopressin alone ( $P < .01$ ), and 2 of 6 with both. It is not clear whether the physiologic and outcome differences in this model were related to developmental issues (eg, pediatric versus adult) or the pathogenesis of the arrest (eg, VF versus asphyxia). No published studies presented evidence clearly favoring epinephrine over vasopressin therapy in either preclinical or clinical settings.

## EVALUATION AND DEBATE

Long-term survival after CPR with epinephrine therapy is disappointing. There is increasing evidence from both laboratory and clinical studies that vasopressin may be a promising alternative vasopressor during cardiac arrest and resuscitation. Vasopressin has been administered safely and effectively in humans to treat clinical conditions requiring vasoconstriction (eg, bleeding esophageal varices and abdominal angiography), even in children with shock in the ICU. Since 1992, several laboratory studies have demonstrated the beneficial physiologic, ROSC, and short-term survival effects of vasopressin in cardiac arrest.<sup>36,41,43-56,62-70,73</sup> For shock-resistant VF vasopressin may improve vital organ blood flow and cerebral perfusion more than epinephrine. Data from animal studies comparing vasopressin with epinephrine are encouraging for improved CPR physiology but raise concerns about postresuscitation cardiac dysfunction and cerebral blood flow. Theoretically, vasopressin has a desirable profile of vasopressor activity for use in cardiac arrest and CPR, causing selective constriction of resistance vessels in nonvital tissues and preserving blood flow to vital organs. In high doses, it has potent peripheral vasoconstrictor activity, acting by direct stimulation of smooth muscle  $V_1$  receptors without stimulation of  $\beta$ -adrenergic receptors. Increased cerebral blood flow during CPR with vasopressin may be beneficial in some circumstances but detrimental in others, and there is a potential risk of cerebral edema or hemorrhage after ROSC. A synthesis of accumulated knowledge from preclinical and clinical cardiac arrest studies suggests that administration of a single pressor agent at the time of arrest is unlikely to have statistically significant effects on long-term outcome. Intense systemic vasoconstriction during early CPR and resuscitation may be critically important for coronary perfusion, but persistence of the same intense vasoconstrictive effects during postresuscitation myocardial ischemia and dysfunction may be dele-

terious. The half-life of vasopressin in the intact circulation is 10 to 20 minutes and at least 5 minutes during CPR,<sup>41</sup> substantially longer than that of epinephrine. Dosing regimens and the half-life of exogenous vasopressin in the human cardiac arrest setting have not been adequately studied, precluding evidence-based recommendations for administration interval or number of doses to administer. Participants suggested that a pressor “cocktail” titrated to balance pharmacologic stimulation with the evolving needs of the individual patient is most likely necessary. Targets for vasopressor therapy during CPR and postresuscitation management, including target patient selection and target physiologic response monitoring, warrant further attention and study. Concern was expressed about the potential for sustained vasoconstrictive effects with use of vasopressin compared with epinephrine because of the longer biologic half-life of vasopressin.

In most of the reported preclinical studies, vasopressin was administered before defibrillation was attempted, which is not directly applicable to current ACLS clinical practice. Studies were not designed to definitively assess ROSC outcome, and long-term survival was rarely addressed. Critical outcomes (eg, hemodynamic effect, ROSC, survival to admission, survival to discharge, and intact neurologic status) are important determinants of Emergency Cardiac Care Committee guideline recommendations. The 1 published prospective, randomized clinical study had a short median emergency physician ACLS response interval (6 minutes), and the equivalence of 40 units of vasopressin and 1 mg epinephrine was questioned. The availability of only a small number of peer-reviewed, published human cases (n = 38) at the time of the conference limits our ability to advocate vasopressin as a definitive treatment of choice, even for shock-refractory VF. Larger randomized, double-blinded trials comparing vasopressin with epinephrine therapy in in-hospital (n = 201)<sup>59</sup> and out-of-hospital (n = 30)<sup>74</sup> adult cardiac arrest are being conducted, and preliminary data was shared with the panel. Definitive data on long-term survival and neurologic outcome advantage, dosing sequence and frequency, and human data on rhythms other than shock-refractory VF is lacking. Detrimental long-term survival or neurologic effects will be difficult to demonstrate because the baseline intact survival rate for this arrest population is only 3% to 5%. Nonetheless, no preclinical or clinical studies directly comparing epinephrine with vasopressin therapy favor epinephrine therapy. Vasopressin is relatively inexpensive, widely

available, easy to store and transport, and accepted as a therapy for other conditions requiring vasoconstriction. Vasopressin has demonstrated efficacy in special resuscitation circumstances, including hypothermia, anesthesia-associated arrest, hypovolemia, and vasodilatory shock. Further study of the optimal dosage, dose regimens, use in arrests other than shock-refractory VF, and its relationship to other pressor agents is warranted. Populations with increased risk and those most likely to benefit need to be identified. No human data on the use of vasopressin in the specific setting of pediatric or neonatal cardiac arrest have been published. The panel discussed the potential impact of the class of recommendation (Indeterminate, Class IIa, or Class IIb) on the universal and pulseless arrest algorithms and agreed that recommendations should neither preclude nor encourage the use of vasopressin for rhythms other than shock-refractory VF in adults at this time.

#### PROPOSED GUIDELINES

Based on discussion and debate at the Evidence Evaluation and Guidelines 2000 Conferences, it was believed that vasopressin is an effective vasopressor and can be used as an alternative to epinephrine for the treatment of adult shock-refractory VF (Class IIb). Vasopressin may be effective in patients with asystole or pulseless electrical activity as well. However, as of 2000, we lack sufficient data to support an active recommendation to use vasopressin (Class Indeterminate). Vasopressin should be effective in patients who remain in cardiac arrest after treatment with epinephrine, but there is inadequate data to evaluate the efficacy and safety of vasopressin in these patients (Class Indeterminate). There is inadequate data to evaluate the efficacy and safety of vasopressin in infants and children at this time (Class Indeterminate).

Vasopressin is a promising adjunct or alternative pressor to epinephrine for the treatment of cardiac arrest (Class Indeterminate). Vasopressin should be considered an alternative pressor to epinephrine for the treatment of shock-refractory, VF-induced cardiac arrest in adults (Class IIb). Dosing regimens and the half-life of exogenous vasopressin in human cardiac arrest have not been adequately studied, precluding evidence-based recommendations for administration interval or number of doses to administer. The available data are inadequate to evaluate the efficacy and safety of vasopressin in the treatment of cardiac arrest in infants and children (Class Indeterminate).

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ADDITIONAL RESOURCES

Topic 2: Use of Epinephrine in Infants and Children

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Topic 3: Use of Vasopressin

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