PRESSOR DRUGS IN THE TREATMENT OF CARDIAC ARREST

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The importance of vital organ perfusion in patients suffering cardiac arrest makes arterial vasomotor tone, and the resultant perfusion pressure, critical in resuscitation from sudden death. After failure of countershock, ventilation, and oxygenation, the target organ for resuscitative pharmacotherapy becomes the arterial vascular smooth muscle cell. Selective stimulation of various vascular smooth muscle cell surface receptors is accomplished through administration of exogenous agents with the intention of altering blood flow away from nonvital organ beds toward the myocardium and brain.

Although there are multiple mechanisms that may affect arterial vascular tone, historically, the therapy most commonly used has been catecholamine-induced adrenergic receptor stimulation, with catecholamine epinephrine being the commonest drug used. Over the last decade, however, it has become widely known that the utility of epinephrine during cardiopulmonary resuscitation is undefined. There always has been concern that its β-receptor–mediated effects, in particular its effects on myocardial oxygen consumption, actually may be deleterious in the setting of ischemia. Of particular note, so-called “high-dose” epinephrine therapy, which had appeared effective with respect to return of spontaneous circulation (ROSC) in laboratory models and uncontrolled clinical trials, has not been found to improve neurologic outcome in prospective controlled clinical trials. This has led to research into alternative agents, in particular nonadrenergic vasoactive peptides. Other agents—new and old—appear promising. These include α-methyl-norepinephrine and phenylephrine.

Recently, vasopressin has been the focus of considerable research effort. In laboratory models of cardiopulmonary arrest, vasopressin improves vital organ blood flow, cerebral oxygen delivery, rate of ROSC, and neurologic recovery compared with epinephrine. In a single study of patients with out-of-hospital ventricular fibrillation (VF), a larger proportion of patients treated with vasopressin survived 24 hours compared with epinephrine. Currently, a large trial of out-of-hospital cardiac arrest patients being treated with vasopressin versus epinephrine is ongoing in Germany, Austria, and Switzerland. The most recent cardiopulmonary resuscitation (CPR) guidelines of the American Heart Association (AHA) and European Resuscitation Council...
recommend 40 units vasopressin or 1 mg epi-
nephrine intravenously in patients refractory
to electrical countershock.

HISTORY

The history of pressor drugs and adrenergic
agonists is, to a great extent, synonymous
with research on epinephrine and its uses. It
was observed in the mid-18th century that
extracts of the suprarenal gland raised blood
pressure. Starting in 1894, Szymonowicz, Cy-
bulski, and Oliver and Schafer used adrenal
gland extracts to enhance peripheral vasocon-
striction and latter to revive asystolic isolated
animal hearts. In 1896, Gottlieb used adrenal
gland extract and thoracic compressions to
resuscitate an asystolic rabbit and proposed
its use to treat cardiac arrest in humans.

During the first 60 years of this century,
epinephrine was used as a vasopressor, with
anecdotal use during cardiac arrest. Starting
in the early 1960s, Redding and Pearson un-
dertook a series of experiments that are the
foundation of modern research on resuscita-
tion. A number of their studies demonstrated
the utility of vasoactive amines in the treat-
ment of cardiac arrest of more than a few
minutes duration. Many of their recommen-
dations were incorporated in the AHA guide-
lines of 1974.

BASIC SCIENCE

The autonomic nervous system is dedicated
to maintenance of homeostasis through neu-
roendocrine changes in visceral function. It is
divided into afferent and effector limbs, and
many autonomic nerves are organized into
regional plexuses located outside the central
nervous system (CNS). The efferent limb of
the autonomic nervous system consists of
sympathetic and parasympathetic divisions.
Drugs may affect the autonomic nervous sys-
tem at multiple locations, including the af-
ferent limb, the CNS, ganglia, and peripheral
innervations of visceral structures.

Preganglionic autonomic fibers, postgangli-
onic parasympathetic fibers, and some post-
ganglionic sympathetic fibers all respond to
the neurotransmitter acetylcholine and are
termed cholinergic fibers. Most postganglionic
sympathetic fibers are termed adrenergic be-
cause the neurotransmitter is noradrenaline
(norepinephrine). Stimulation of adrenergic
or cholinergic tissue receptors, either through
autonomic outflow or drug administration,
results in typical end-organ responses. Gener-
ally, stimulation of one limb of the autonomic
nervous system, either the parasympathetic
or sympathetic, antagonizes the effects of the
other. It is not known, however, if this rela-
tionship is significant during cardiac arrest,
which is a state of extreme sympathetic stim-
ulation. Modulation of parasympathetic tone,
for instance, has not been demonstrated to
be important during cardiac arrest, and
atropine may have limited use in treatment
of adult VF.

The binding of an adrenergic drug to its
receptor causes characteristic changes in the
intracellular concentration of second-messen-
ger molecules, which result in the physiologic
effects characteristic of the drug. Second mes-
sengers include cyclic adenosine monophos-
phate (cAMP), phosphatidylinositol, and cal-
cium. Epinephrine, produced by the chromaffin
cells of the adrenal medulla, is stored in chro-
maffin granules. These cells are innervated by
the sympathetic nervous system and release
stored epinephrine in response to stimulation.
The degree of sympathetic outflow is a func-
tion of homeostatic feedback mechanisms and
is responsive to various stimuli, such as
changes in blood pressure, tissue oxygen-
ation, and environmental stress. The most im-
portant endogenous neurohumoral event in
cardiac arrest is the release of adrenomedul-
ary catecholamines as a massive sympathetic
response to extreme hypotension. The role of
exogenous epinephrine during early treat-
ment of sudden death when endogenous lev-
els are extraordinarily high is unknown.

The first systematic study of adrenergic ag-
onists was performed by Ahlquist, who ex-
amined the effects of sympathomimetic
amines on tissues and delineated two distinct
classes of physiologic effect. The first, which
he termed α-effects, were excitatory; the
second, termed β-effects, were inhibitory.
Stimulation of α-receptors typically caused
vasoconstriction, whereas stimulation of β-receptors causes vasodilation. Ahlquist also described an order of potency in each class in descending order for the excitatory α-receptor, were epinephrine, norepinephrine, and isoproterenol; for the inhibitory β-receptor the order was isoproterenol, epinephrine, and norepinephrine.

With apparent contradiction, cardiac stimulation was found to be an inhibitory β-receptor stimulation. The β-subtype was later subdivided into smaller classes, β1 and β2, with different physiologic effects. Stimulation with β1-agonists increased cardiac inotropy and chronotropy.

The pathophysiology and pharmacology of the autonomic nervous system during global ischemia and CPR have not been studied beyond simple measurement of levels of circulating hormone. Other than a dramatic increase in circulating catecholamines, it is not known how global ischemia affects autonomic outflow and target organ receptor number and function.

**MECHANISM OF ACTION**

The treatment of cardiac arrest with adrenergic agonists predated understanding of their possible mechanisms of action, and our knowledge of these drugs remains incomplete. Although during spontaneous circulation, sympathetic stimulation results in diverse autonomic effects, including changes in inotropy and chronotropy, the importance of the processes during the treatment of cardiac arrest remains unknown.

Cardiopulmonary resuscitation is a state of extreme global ischemia, tissue hypoxia, and acidosis. Successful resuscitation depends on reversal of organ hypoxia by improving the supply and demand equilibrium for oxygen. Studies in animal models indicate that the fibrillating myocardium may require blood flow in excess of 40 to 50 mL/min × 100 g to achieve ROSC. Because the oxygen debt increases with the duration of cardiac arrest, greater blood flows are likely to be required later in resuscitation. Importantly, cellular changes late in resuscitation may interfere with oxygen utilization within the mitochondria and mask the relationship between blood flow and outcome.

Myocardial blood flows during CPR fall rapidly below the needs of the myocardium as the time from loss of circulation increases. Pressor drugs are administered during CPR to raise arterial pressure and redistribute blood flow to vital organs. Studies in animal models and patients have shown a high correlation between the relaxation phase aortic-to-right atrial pressure gradient, myocardial blood flow and ROSC. It is now widely accepted that this gradient is the de facto coronary perfusion pressure during standard external CPR. External chest compression alone is often unable to achieve a perfusion gradient of sufficient magnitude to achieve ROSC after the first few minutes of cardiac arrest, possibly because vascular smooth muscle cell hypoxia and loss of cellular energy charge cause a diffuse vasorelaxation. Without exogenous agents, a large fraction of forward flow is directed to organs other than the brain and heart.

Redding and Pearson observed that CPR was only minimally effective without administration of adrenergic agonists. In one study, all animals treated with methoxamine or epinephrine had ROSC, while the pure β-agonist isoproterenol was less effective than placebo. More recent studies have supported the conclusion that vasoconstriction resulting in increased aortic pressure in the relaxation phase may be the principal mechanism of action by which vasopressor therapy achieves ROSC.

Redding and Pearson’s research suggested that α-adrenergic stimulation was of critical importance, while stimulation of β-receptors was not beneficial, possibly even detrimental. In a landmark series of studies, Yakaitis et al and Otto et al examined the effect of selective combinations of α- and β-receptor stimulation and blockade on resuscitation in an asphyxial–electromechanical dissociation (EMD) model of cardiac arrest. Their work supported the hypothesis that peripheral α-receptor stimulation is crucial to the efficacy of adrenergic agents and that epinephrine’s β-agonism was of little therapeutic benefit. Recently, Ditchey and Slinker found that prearrest β-receptor blockade resulted in sig-
nificantly higher aortic and coronary perfusion pressures.

Efficacy of Pressors

Although Crile and Dolley\textsuperscript{24} had observed that epinephrine improved their ability to restore a heartbeat to dogs in cardiac arrest around the turn of the century, the utility of sympathomimetic amines in the treatment of cardiac arrest was first systematically studied by Redding and Pearson starting in the 1960s.\textsuperscript{20, 25–27} Research standards at the time, combined with orientation toward treatment of cardiovascular collapse secondary to anesthetic induction, resulted in studies that were limited in size and had a number of methodological limitations. Nonetheless, they convincingly demonstrated the efficacy of adrenergic agents as adjuncts during CPR, a finding that continues to be supported by laboratory research to this day. Redding and Pearson\textsuperscript{26} found epinephrine-treated animals were up to 9 times more likely to achieve ROSC than those treated with placebo. Indeed, in most laboratory models there is ROSC after the first few minutes of cardiac arrest by external chest compression alone. Addition of pressor drugs extends the window of efficacy for external chest compression to at least 15 minutes.\textsuperscript{28} Although clinical trials have not clearly demonstrated the efficacy of epinephrine, the preponderance of laboratory studies and direct comparison in controlled clinical trials make choice of a specific drug difficult.

A wide range of adrenergic-receptor agonists is available. Currently, the mixed $\alpha$- and $\beta$-agonist epinephrine is used almost universally. Pure $\alpha$-agonists, such as methoxamine and phenylephrine, have been studied and occasionally are used clinically (Table 1). The $\beta$-receptor-agonist isoproterenol was once popular but is now almost never used in the treatment of cardiac arrest because of concern that it may decrease perfusion.

There are also a number of vasoactive peptides available; however, at this time, only vasopressin is used clinically.\textsuperscript{31}

Individual Adrenergic Agents

A number of sympathomimetic agonists have been considered in therapy for cardiac arrest. Typically, these drugs have undergone extensive evaluation in animals and humans during spontaneous circulation,\textsuperscript{29, 30} whereas assessment in cardiac arrest has been incomplete. The paucity of laboratory studies and direct comparison in controlled clinical trials make choice of a specific drug difficult.

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Epinephrine

Epinephrine is the best studied and most widely administered adrenergic agonist used for the treatment of cardiac arrest. Epinephrine stimulates $\alpha_1$- and $\alpha_2$-receptors almost equally,\textsuperscript{32} and $\beta_1$- and $\beta_2$-receptors in a ratio of approximately 1 to 4.\textsuperscript{29–30, 33–34}

There are no prospective clinical trials that demonstrate the efficacy of epinephrine in improving the outcome of patients suffering cardiac arrest. Since at least the 1970s, epi-
Table 1. DATA FROM RANDOMIZED CLINICAL TRIALS COMPARING STANDARD- WITH HIGH-DOSE EPINEPHRINE

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (no)</th>
<th>Dose (mg)</th>
<th>ROSC (%)</th>
<th>Discharge (%)</th>
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<tbody>
<tr>
<td></td>
<td>HDE</td>
<td>SDE</td>
<td>HDE</td>
<td>SDE</td>
</tr>
<tr>
<td>Abrams</td>
<td>1456</td>
<td>1459</td>
<td>5, 10, 15</td>
<td>1</td>
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<tr>
<td>Brown</td>
<td>648</td>
<td>632</td>
<td>14</td>
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<tr>
<td>Callaham</td>
<td>286</td>
<td>260</td>
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<td>Choux</td>
<td>271</td>
<td>265</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Gueugniaud</td>
<td>1677</td>
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<td>1</td>
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<tr>
<td>Lindner</td>
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<td>1</td>
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<td>1</td>
</tr>
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<td>Sherman</td>
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<td>7</td>
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<tr>
<td>Stiell</td>
<td>317</td>
<td>333</td>
<td>7</td>
<td>1</td>
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<tr>
<td>Totals</td>
<td>4780</td>
<td>4717</td>
<td>1129 (24)</td>
<td>1003 (21)</td>
</tr>
</tbody>
</table>

HDE = high-dose epinephrine; SDE = standard-dose epinephrine; ROSC = return of spontaneous circulation.

*These data are survival at 15 days; discharge data were not available for this study.

Epinephrine has been administered almost universally to patients who have failed basic life support and electrical countershock. This de facto “standard” has made performance of placebo-controlled clinical trials extremely difficult. There is, however, a report of a study in which this was performed. Woodhouse et al assigned patients in asystole, or who had failed countershock, to 10 mg epinephrine or placebo. Another group was given a standard 1-mg dose of epinephrine. The rates of immediate survival and hospital discharge were similar in each group, and these investigators concluded that the use of epinephrine makes “no difference to the outcome of asystole or after two countershocks in those remaining in ventricular fibrillation.” Woodhouse et al did, however, note that a “change of rhythm to a potentially treatable rhythm occurred more significantly in the 1-mg and 10-mg groups,” compared with placebo.

A number of limitations raise doubts about these conclusions. Thirty-eight percent of eligible patients were not randomized because of the concerns of the supervising physicians about entering into the placebo arm of the study. Most likely, this study reflects the difficulty of studying therapies that are also predictors of poor prognosis because they are markers of downtime.

There are reasons to be concerned that epinephrine salutary effect on perfusion and the rate of ROSC are counterbalanced by the toxicity of its β-adrenergic effects. Tang et al have shown in a series of experiments that use of epinephrine can result in postresuscitation myocardial dysfunction, including stone heart. Berg et al found a worse 24-hour survival in one animal model. Failure of the randomized clinical trials of high-dose epinephrine to demonstrate an improvement in outcome are also worrisome as effective therapies usually have a detectable dose-response relationship. A reasonable synthesis of the homogenous laboratory data and the heterogenous clinical data is that epinephrine is effective in restoring circulation in patients who have failed CPR and countershock, but that this is at the cost of occasionally significant postresuscitation toxicity.

Pharmacology of Epinephrine in Cardiac Arrest

The physiochemistry, bioavailability, volumes of distribution, protein binding, metabolism, elimination, and other standard pharmacologic indices have not been delineated for epinephrine during CPR. Almost all that is known about this drug is from laboratory models and humans with spontaneous circulation. It has been so common to extrapolate from the spontaneous circulation to the arrested state that physicians often forget that this has little scientific basis.

Because the common United States formulations of epinephrine as hydrochloride have pH values ranging from 2.5 to 5.0, a poten-
tially important interaction may occur between epinephrine and alkalinizing agents. The AHA guidelines have stated that “epinephrine is inactivated in alkaline solutions and should never be mixed with sodium bicarbonate.” Although the use of sodium bicarbonate in cardiac arrest may be declining, this potential incompatibility remains important, especially for patients with only a single route of intravenous access. In one study, the biological activity of epinephrine decreased 13% after injection through a cannula containing 0.6 mol/L sodium bicarbonate. While the absolute dictum against mixing of epinephrine and bicarbonate does not seem to be supported by the available data, it seems prudent to avoid the theoretical stoichiometric inactivation if two routes of administration are available.

The multidose vial of 30 mL of 1 mg/mL epinephrine commonly used in the United States for high-dose epinephrine therapy contains 0.15% sodium bisulfite. Some decrement in concentration, perhaps 10%, may occur with this particular formulation after storage. There are also unpublished reports of up to 30% variability in epinephrine concentrations in the standard 1-mg bolus ampules, with a tendency toward less than 1 mg. Intravenous administration during CPR is a dynamic and poorly quantified process in which drugs are injected rapidly and the admixture space, volume of the intravenous tubing, and admixture site are variable. Whenever possible, it is perhaps best to administer epinephrine to some therapeutic endpoint, such as the change in aortic pressure.

**Epinephrine and Ventricular Fibrillation**

Redding and Pearson noted that dogs in VF were more quickly defibrillated after epinephrine therapy, and Yakaitis et al found the drug important for achieving ROSC after countershock. “After two minutes of fibrillation, epinephrine [becomes] increasingly important for restoration of circulation. The technique of immediate countershock was effective [only] for episodes of fibrillation limited to approximately three minutes.”

Niemann et al studied the need for perfusion before defibrillation in a laboratory model with a duration of cardiac arrest comparable to that seen in human out-of-hospital sudden death. Animals were given either immediate countershock or were treated with epinephrine followed by 5 minutes of CPR before countershock. Animals that received epinephrine had a higher rate of ROSC despite longer arrest times. Animals countershocked without adrenergic therapy developed pulseless electrical activity (PEA).

**Epinephrine and Neurologic Outcome**

Adrenergic agonists improve cerebral blood flow in laboratory models. Because the time from onset of arrest to ROSC is the primary determinant of neurologic outcome, early use of drugs, such as epinephrine, may shorten arrest time and thus improve outcome. While preliminary reports from animal models indicate that adrenergic drugs may have a direct neuroprotective effect, other studies do not find this effect. Of particular concern, postreperfusion myocardial dysfunction may contribute to a secondary CNS injury. There has been concern that restoration of spontaneous circulation in patients who have suffered irreparable CNS injury may result in a significant burden on families and society. In particular, high-dose epinephrine, with its potential to resuscitate patients after prolonged arrest, raises the concern that patients with irreversible brain damage may be revived. Although methodologically limited studies have purported to detect this phenomenon, meta-analysis of the high-dose epinephrine randomized controlled trials (RCTs) has failed to detect this.

**Toxicity of Epinephrine**

The potential toxicity of epinephrine during and after cardiac arrest has been of concern since it was advocated as therapy almost 40 years ago, largely as a result of reports of the alarming effects of accidental epinephrine overdoses in patients with intact circulations. The importance of these effects to
patients with arrested circulation is unclear. The severe hypertension that occurs with epinephrine overdose in intact patients is not applicable during cardiac arrest, whereas increased oxygen use unmatched by increased perfusion would be deleterious. Early concerns that epinephrine might trigger intractable ventricular tachydysrhythmias in cardiac arrest have not been substantiated; however, this may be because these events are difficult to separate from primary VF.

In some studies, epinephrine increases myocardial oxygen consumption more than supply,\textsuperscript{50–52} and deleterious changes in the ratio of endocardial to epicardial blood flow and in the distribution of pulmonary blood flow also have been reported.\textsuperscript{53, 54} The importance of these effects during resuscitation from cardiac arrest is unclear because they have been demonstrated in some animal models and patients but not in others.\textsuperscript{45, 50, 55} The drug’s clear ability to improve the rate of ROSC indicates that, overall, these potential toxicities are more than compensated by improved perfusion.\textsuperscript{56}

A pattern of myocardial injury, termed contraction-band necrosis, has been associated with exposure to high plasma levels of catecholamines.\textsuperscript{57–58} β-Receptor blockade appears to protect the myocardium from contraction-band necrosis, supporting the hypothesis that pure α-Receptor agonists, such as phenylephrine, may be attractive agents. Recently, Tang et al.\textsuperscript{59} have demonstrated that compared with alternative agents, epinephrine is correlated with decrements in myocardial function during the postresuscitation period. This has particular import clinically as it may contribute to the refractory shock that often kills patients who have been resuscitated from cardiac arrest.

During spontaneous circulation, catecholamines may also injure the vascular system,\textsuperscript{60–61} and it is reasonable to conclude that the high doses used in the treatment of cardiac arrest may injure the vasculature. Although this injury also may contribute to postreperfusion shock, it has not been well studied.

Epinephrine has a well-described stimulatory effect on platelet aggregation. This is particularly worrisome in the treatment of sudden cardiac death as a substantial fraction of these patients have acute coronary occlusion that results, at least in part, from formation of a coronary thrombus. Platelet aggregation also may play a role in the no reflow phenomena, which is felt to contribute to the CNS injury of postanoxic encephalopathy. The effect of epinephrine on platelets is one of the drug’s least attractive pharmacologic properties.

The potential of epinephrine to harm pulmonary function has received considerable attention. Pulmonary arteriovenous admixture and alveolar dead space may increase after epinephrine administration.\textsuperscript{62} In the laboratory, this may cause relative arterial hypoxia and hypercarbia.\textsuperscript{63} Treatment with the α-agonist methoxamine apparently does not produce similar changes, suggesting that epinephrine may mediate this effect by way of β-agonism. Clinical experience, however, indicates that such toxicity is hypothetical, as arterial hypocarbia and increased arterial O\textsubscript{2} content are the norm during CPR in humans.

There is long-standing concern that administration of epinephrine during resuscitation might result in untoward effects during the important postresuscitation period.\textsuperscript{64} Metaanalysis of the high-dose epinephrine RCTs supports this concern as it indicates that higher dosages of epinephrine may decrease survival slightly. Again, these concerns have focused on β-receptor–mediated injury to the myocardium, vasculature, and some formed elements of blood.\textsuperscript{65–66}

Patients resuscitated after cardiac arrest of relatively short duration often manifest a brief period of hypertension, most probably from residual epinephrine of adrenal or exogenous origin. In patients who have received large amounts of exogenous epinephrine, hypertension may reach alarming levels and may be associated with tachydysrhythmias. This hypersympathetic state lasts only a few minutes and usually is supplanted by hypotension. Failure to treat this hypotension may result in secondary organ injury.

**Dosage of Epinephrine in Cardiac Arrest**

Few of the early investigations of epinephrine in cardiac arrest addressed the issue of
dosage, with many studies using a single dose independent of body weight. In 1906, Crile and Dolley\textsuperscript{24} gave “one to two cubic centimeters [mL] of 1–1000 solution of adrenaline” to dogs. This solution was adrenaline chloride, and the dose has been estimated to have been comparable to approximately 0.4 mg/kg. In their early work, Redding and Pearson\textsuperscript{27} gave a dose of 1.0 mg and found it to be effective in dogs weighing approximately 10 kg, equivalent to 0.1 mg/kg. In commenting on the use of epinephrine use in patients, their 1-mg initial dose was described as “satisfactory,” and it was recommended that this be the “standard.” Some patients, however, required either a second 1-mg dose or a 2-mg total dose.\textsuperscript{25}

In a 70-kg patient, Pearson and Redding’s\textsuperscript{25} 1.0-mg dose is equal to 0.014 mg/kg, or approximately an order of magnitude less on a mg/kg basis than in their animal studies. Interestingly, they mention that 1 mg was used “with benefit in children down to 18 months of age.”\textsuperscript{25} A child of this age would weigh approximately 12 kg, and would have received a dose of approximately 0.083 mg/kg, almost 6 times the adult 1-mg dosage. Historically, the 1-mg dose suggested by Pearson and Redding was considered massive, because much smaller doses were known to be dangerous in patients with intact circulation. Indeed, they were “criticized by some for employing such a large dose.”

Between the mid-1960s and the 1980s, there were few laboratory studies with alternative dosages of epinephrine. The first, by Redding and Pearson,\textsuperscript{67} used a total dose of 0.2 mg. The second, by Jude et al\textsuperscript{68} in 1968, used 0.02 and 0.08 mg/kg and found that the arteriovenous pressure gradient was doubled by the higher dose. In the third study,\textsuperscript{69} a dose of 0.05 mg/kg produced increased cerebral and myocardial blood flows but not to levels considered necessary to meet the needs of the myocardium in early fibrillation. Other than these studies, the possibility of a dose-response curve for adrenergic agonists during CPR was largely ignored.

In 1985, Kosnik et al\textsuperscript{70} reported the first laboratory study to evaluate the dose-response relationship for epinephrine during CPR. They administered 0.015, 0.045, 0.075, and 0.15 mg/kg of epinephrine and measured hemodynamic properties, such as aortic diastolic and coronary perfusion pressures. Although the results were not statistically significant, they did show that only the two higher doses raised and maintained aortic diastolic pressure to approximately 30 mm Hg for 4 minutes. Shortly thereafter, Ralston et al\textsuperscript{71} demonstrated improved resuscitation rates in animals given progressively higher doses of epinephrine. They found that intravenous doses of 0.001, 0.003, 0.01, 0.03, and 0.1 mg/kg produced resuscitation rates of 0%, 10%, 40%, 80%, and 90%, respectively. Endotracheal epinephrine doses, an order of magnitude higher, produced similar results. These results were important because they clearly demonstrated that dose-response curves could be developed for adrenergic agonists during CPR, and that the optimal dose might be much larger than the standard dose of 1 mg.

Brown et al\textsuperscript{72–73} systematically evaluated the effect of epinephrine and other vasopressors on vital organ blood flow during CPR. These studies combined a radiolabeled-microsphere technique for measurement of myocardial and cerebral blood flows with simultaneous measurement of physiologic variables, such as vital organ perfusion pressures, oxygen delivery, and consumption.

These investigators studied the effect of epinephrine, in doses of 0.02, 0.2, and 2.0 mg/kg, on myocardial and cerebral blood flow.\textsuperscript{72–73} Administration of 0.2 mg/kg was associated with significantly greater organ blood flows than the lowest dose. All agonists tested by Brown et al\textsuperscript{72–73} improved myocardial O\textsubscript{2} delivery. Only epinephrine 0.2 mg/kg and nor-epinephrine 0.12 and 0.16 mg/kg, however, increased oxygen delivery to a greater degree than the increase in oxygen consumption. Cerebral blood flow and the rates of ROSC improved with higher dosages for all agonists except methoxamine. While important, the research by Brown et al\textsuperscript{72–73} was not definitive because long-term neurologic survival was not evaluated uniformly. Nevertheless, they demonstrated that there was a rational pharmacologic basis for use of these drugs during CPR. The dose-response curves and pharmacokinetics may be dramatically different from
those during spontaneous circulation, but they are measurable.

Starting in 1987, Lindner et al. evaluated the effects of various epinephrine dosages on hemodynamics and oxygen utilization. The results of these studies generally supported those of Brown et al. in that there was a dose-response relationship between epinephrine and vital organ blood flow and oxygen delivery. Lindner et al., however, found an optimal dosage lower than in the studies by Brown et al.

It seems intuitively reasonable to hypothesize that larger doses of epinephrine may be required as the arrest time increases. Dean et al. addressed this question indirectly when they measured regional blood flow during prolonged resuscitation and found that it declined markedly after 10 to 20 minutes, despite the continuous infusion of vasopressor. Progressively larger infusions of epinephrine were needed to maintain myocardial blood flow late in resuscitation. This suggests that tachyphylaxis to adrenergic agonists occurs or that there is progressive derangement of the CPR circulatory pump mechanism, or both. During the 1980s, laboratory studies indicated that higher doses of epinephrine might be effective in improving perfusion during CPR.

The pharmacology of higher epinephrine doses in humans was first studied by Gonzalez et al. They measured changes in radial artery pressure after intravenous administration of 1, 3, and 5 mg of epinephrine in patients who had failed standard therapy and had been transported to the hospital. Only the highest dose significantly raised relaxation-phase pressure. Paradis et al. compared the standard 1-mg dose with a 0.2-mg/kg dose in patients who had failed conventional therapy and had been transported to the hospital. Only the highest dose significantly raised relaxation-phase pressure. Paradis et al. compared the standard 1-mg dose with a 0.2-mg/kg dose in patients who had failed conventional therapy, including standard dosages of epinephrine. Coronary perfusion pressure increased only after administration of high-dose epinephrine. Because these studies were performed late in resuscitation, their applicability to the more important early therapy remains unclear. They do indicate, however, that continued use of a 1-mg dose late in resuscitative efforts is without scientific basis.

Early human studies of high-dose epinephrine, which tended to be performed in patients who had failed conventional doses, reported improvements in variables such as coronary perfusion pressure and the rate of ROSC. In some of these studies, and many of the case reports, the patients’ ROSC was temporally related to administration of high-dose epinephrine.

In the first well-designed, large clinical trial of high-dose epinephrine, Brown et al. and associates compared 0.02 mg/kg with 0.2 mg/kg epinephrine in 1280 patients suffering out-of-hospital cardiac arrest. This study found no significant difference in clinical outcome between the two groups. In patients with a witnessed arrest, it took approximately 17 minutes between the onset of arrest and the first epinephrine administration. Patients with unwitnessed arrest must have received the drug even later. The few patients who received their first dose of epinephrine within 10 minutes of cardiac arrest had a trend toward a higher rate of survival to hospital discharge (23% versus 11%). Patients with EMD had ROSC rates of 47% with high-dose epinephrine versus 33% with standard dose. These were post hoc subgroups, so the results should not be considered persuasive. There had been concern that administration of high-dose epinephrine might result in an increase in survivors with severe neurologic impairment, but this did not occur. The results in this study did not reach statistical significance, nor do they have statistical power. Therefore, it is not possible, using this data set, to determine if high-dose epinephrine is better, worse, or the same as standard dose.

Callaham et al. performed a randomized, prospective, double-blind clinical trial comparing standard-dose epinephrine and high-dose epinephrine and norepinephrine in the treatment of prehospital cardiac arrest. They prospectively identified the outcome variables of interest as ROSC in the field, admission to hospital, hospital discharge, and Cerebral Performance Category score. Eight hundred sixteen patients met inclusion criteria. Thirteen percent of patients receiving high-dose epinephrine regained a pulse in the field versus 8% of those receiving standard dose. Eighteen percent of patients receiving high-dose epinephrine were admitted to the hospital compared with 10% of patients re-
ceiving a standard dose. Nevertheless, there was no statistical difference in hospital discharge. No benefit of norepinephrine compared with high-dose epinephrine was found. High-dose epinephrine did not result in longer hospital or critical care unit stays. These investigators concluded that high-dose epinephrine significantly improves the rate of ROSC and hospital admission without increasing complications.

Of note is that in the entire study population, 63% of the survivors were among the 11% of patients who were defibrillated by first responders. Therapies that are administered after failure of defibrillation are difficult to study because the sample sizes needed to demonstrate efficacy, or lack of efficacy, are so large.

The Brain Resuscitation Clinical Trial group (BRCT) studied more than 2000 cardiac arrest patients. These patients had either failed electrical countershock or presented with PEA or asystole. Patients were randomly assigned to three doses of either standard or escalating high-dose epinephrine (5 mg, 10 mg, and 15 mg). ROSC occurred in 28% of patients receiving standard dose versus 31% of those receiving escalating high-dose epinephrine. Again, however, high-dose epinephrine resulted in a significant improvement in short-term resuscitation, but did not show a beneficial effect on long-term outcome.

There have now been more than half a dozen RCTs of high-dose epinephrine. Two recent meta-analyses have attempted to make some sense of this pool of data. Vandycke and Martens identified and reviewed 5 clinical trials with a total n-value of 6339, whereas Paradis et al chose broader inclusion criteria and reviewed nine studies for a total n-value of 9497. Paradis et al notes that there is a small increase in ROSC in the high-dose epinephrine versus standard-dose epinephrine groups, with a number needed to treat of 27, that is, use of high-dose epinephrine versus standard-dose epinephrine will cause an additional 1 ROSC per 27 patients treated (see Table 1); however, neither meta-analysis demonstrated an increase in survival to hospital discharge or improvement in neurological outcome, and Paradis et al’s analysis indicated that high-dose epinephrine may slightly decrease the odds of survival.

**ALTERNATIVE CATECHOLAMINES: PHENYLEPHRINE**

Laboratory studies indicate that it is epinephrine α-adrenergic stimulation that appears to be important in cardiac arrest. This makes pure α-adrenergic agents, such as phenylephrine or methoxamine, attractive drugs in the treatment of cardiac arrest. Because of the longer half-life of methoxamine, which can result in organ hypoperfusion postresuscitation, the authors limit their discussion of alternative catecholamines to phenylephrine.

Phenylephrine is a short-acting selective α-adrenergic agonist. It is used as a pressor during anesthesia in patients with spontaneous circulation. Its receptor profile and short half-life make it a theoretically attractive drug for the treatment of cardiac arrest. The potential of this drug to increase aortic pressure without significant myocardial excitation may be optimal for entities such as VF. Its short half-life provides flexibility in the postresuscitation period during which many patients may not need pressor support.

Animal studies indicate that, compared with placebo, phenylephrine raises CPR perfusion pressure, the fraction of animals with ROSC, and short-term survival. The theoretical benefits of selective α-agonism, as compared with a mixed α- and β-agonist, such as epinephrine, however, have not been demonstrated clearly. Nevertheless, in situations in which excessive β-receptor stimulation might be contraindicated, such as cardiac arrest complicating myocardial infarction, phenylephrine is an attractive pressor.

The first studies of phenylephrine were undertaken by Pearson and Redding. Their realization that vasoconstriction was important in achieving ROSC led them to study all available pressors, including phenylephrine, metaraminol, and methoxamine. In their asphyxial-EMD model, 10 mg of intracardiac phenylephrine, a dose selected on “theoretical grounds and pilot experiments,” resulted in
ROSC in 80% to 90% of animals. In a VF model, they achieved 100% ROSC.

Joyce et al administered 5 mg of phenylephrine to dogs in an asphyxial-EMD model and found that it raised aortic diastolic pressure and that all animals were resuscitated. Holmes et al, however, found that a dose of 0.05 mg/kg actually lowered cerebral blood flow compared with placebo. Brown et al studied the effect of phenylephrine on myocardial and cerebral blood flows in a porcine VF model and found that dosages of 0.1 and 1.0 mg/kg did not significantly improve hemodynamics. A dosage of 10 mg/kg improved aortic diastolic pressure and central blood flow by amounts similar to those with a high dose of epinephrine. Gervais et al and Berkowitz et al found that phenylephrine was able to maintain CPR hemodynamics and oxygen utilization as effectively as epinephrine. Gervais et al and Schleien et al, using a model with a very short arrest time, had ROSC in 73% of animals and 100% in a model with 8 minutes of cardiac arrest. Brillman et al had ROSC in 78% of animals using a dose of 10 mg. A subsequent study with the same dose had a 75% ROSC and 50% 24-hour survival. Ditchey and Slinker recently observed that the balance between myocardial oxygen supply and demand during CPR could be improved by administering a combination of phenylephrine and propranolol, and that prearrest β-blockade improved perfusion pressure.

Despite the theoretical advantages of phenylephrine, only a single clinical study has been reported, the interpretation of which is complicated by a crossover design where all patients unresponsive to initial therapy received epinephrine. The ultimate rates of ROSC were 31% and 28% for phenylephrine and epinephrine, respectively. The investigators were of the opinion that there were no adverse reactions in patients who had initially received phenylephrine. Unfortunately, this study also used what may have been subtherapeutic and nonequipressor doses of each drug: 1 mg of phenylephrine and 0.5 mg of epinephrine.

Significant variability in the effective dose in different laboratories precludes recommendation of a specific dosage. An initial dose of 10 mg appears reasonable. Doses as high as 10 mg/kg, have some basis according to the literature, but, until additional clinical trials are performed, the inability to recommend a particular dosage may limit use of phenylephrine. Because this is a generic drug, additional research on its efficacy or dosage is unlikely.

**Vasopressin**

Vasopressin, also termed *antidiuretic hormone*, is a vasoactive peptide with a long evolutionary history. With the emergence of life on land, vasopressin became the mediator of a remarkable regulatory system for the conversation of water. Natural vasopressin forms are nonapeptides with two cysteine residues forming a bridge between positions one and six. The integrity of this disulfide bond is essential for its biological activity, and amino acid substitutions dictate physiologic actions, such as alterations of antidiuretic, or vasopressor function.

Vasopressin acts directly by way of V1-receptors on contractile elements—an effect that can not be reversed by adrenergic blockade or denervation. Previously, vasopressin and its analogues were used to treat hypothalamic diabetes insipidus and bleeding esophageal varices.

Many fundamental endocrine responses of the human body to cardiac arrest and CPR have been investigated in the past 10 years. Circulating endogenous vasopressin concentrations were high in patients undergoing CPR, and levels in successfully resuscitated patients have been shown to be significantly higher than in patients who died. This may indicate that the human body discharges vasopressin in response to epinephrine during cardiac arrest.

In a study of 60 out-of-hospital cardiac arrest patients, parallel increases in plasma vasopressin and endothelin were found only in surviving patients. Both before and after epinephrine administration, plasma epinephrine and norepinephrine concentrations were significantly higher in patients who died when compared with surviving cardiac arrest victims. Thus, plasma concentrations of va-
sopressin may have a more important effect on CPR outcome than previously thought, and prompted several investigations to assess its role for possible CPR management in order to improve CPR management.

Vasopressin In Laboratory Models

During VF, an investigation of three vasopressin dosages (0.2, 0.4, and 0.8 U/kg) compared with the maximum effective dose of 200 µg/kg epinephrine showed that 0.8 U/kg vasopressin increased vital organ blood flow.98 Also, vasopressin significantly improved cerebral oxygen delivery, and VF mean frequency.99 The effects of vasopressin on vital organ blood flow lasted longer than after epinephrine (~4 versus ~1.5 min); significantly more vasopressin animals could be resuscitated, and it did not result in bradycardia after ROSC.100 Interestingly, the combination of vasopressin and epinephrine versus vasopressin only resulted in comparable left ventricular myocardial blood flow, but in significantly decreased cerebral perfusion.101 A rodent study of vasopressin, norepinephrine, and a combination of vasopressin and norepinephrine showed that V₁- and α-adrenergic receptors saturated the same intracellular transduction pathway.102 Although speculative, this mechanism may have hampered nitric oxide release in the cerebral vasculature induced by vasopressin, and therefore, suppressed cerebral perfusion in animals receiving a combination of vasopressin and norepinephrine. These results are striking, because epinephrine selectively spares the cerebral circulation from vasoconstriction when administered during CPR alone.

Vasopressin causes significantly higher vital organ blood flow and cerebral oxygen delivery than epinephrine.98-101 This implies that vasopressin dilated cerebral arterioles and subsequently, resulted in superior brain perfusion throughout the neuraxis. Cerebral blood flow lead to a greater cerebral oxygen consumption but was not the result of increased metabolism as cerebral oxygen extraction fell, and oxygen uptake became independent of oxygen delivery.101 It is unknown whether the increased cerebral blood flow during CPR with vasopressin is beneficial.

Renal and splanchnic perfusion may be critically impaired during94 and after103 successful resuscitation from cardiac arrest. For example, 30 minutes after ROSC, renal and adrenal blood flow were significantly lower in the vasopressin in pigs as compared with the epinephrine group.104 It is unknown whether the vasopressin-mediated changes in blood flow might be deleterious for splanchnic organs, and whether this may contribute to multiorgan failure after ROSC. Furthermore, it is unknown whether a high bolus of vasopressin administered during CPR may result in oliguria or anuria because of its anti-diuretic effects in the postresuscitation phase. In a porcine CPR investigation, vasopressin impaired cephalic mesenteric blood flow during CPR and in the early postresuscitation phase but did not result in an anti-diuretic response.105

Infusion of low-dose dopamine mediated a significant increase in superior mesenteric blood flow after successful CPR with vasopressin by selective vasodilatation of intestinal vessels. Accordingly, administering dopamine may improve gut perfusion, and therefore, may improve gut function in the postresuscitation period.106

In a porcine model simulating prolonged (22 min) advanced cardiac life support, all vasopressin animals had ROSC, whereas all pigs in the epinephrine and saline placebo group died. After 24 hours, the only neurologic deficit was an unsteady gait, which disappeared within another 3 days.107 This observation confirms that in order to achieve full recovery after cardiac arrest, both excellent management of basic and advanced cardiac life support and careful optimization of organ function in the postresuscitation phase are of fundamental importance.108 Laboratory evidence suggests that vasopressin given during CPR may be a superior drug when compared with epinephrine in order to ensure ROSC and neurological outcome.

Route of Administration

In a laboratory model the same dose of intravenous and endobronchial vasopressin
resulted into the same coronary perfusion pressure 4 minutes after drug administration. In contrast, the equipotent endobronchial epinephrine dose is approximately 10 times higher than the intravenous epinephrine dose during CPR. Endobronchial drug administration may be less appropriate in children who suffer cardiac arrest due to respiratory disorders. Accordingly, the intraosseous route has been recommended for pediatric emergency situations. In a porcine investigation, intraosseous versus intravenous vasopressin resulted in comparable vasopressin plasma levels, hemodynamic variables, coronary perfusion pressure, and ROSC rates. The authors’ laboratory studies indicate that the same vasopressin dosage may be administered intravenously, endobronchially, and intraosseously, rendering usage of this vasopressor during CPR simple, rapid, and inexpensive.

Clinical Use In Treatment of Cardiac Arrest

The AHA and European Resuscitation Council continue to recommend repeated administration of epinephrine during advanced cardiac life support, although it is not proven whether repeated epinephrine given during CPR may be effective, or if this strategy may even result in inadvertent catecholamine toxicity. After repeated dosages of vasopressin and epinephrine, coronary perfusion pressure increased only after the first epinephrine injection, but increased after each of three vasopressin injections. Accordingly, all vasopressin animals survived, whereas all pigs resuscitated with epinephrine died.

Long-term survival after cardiac arrest may be determined by the ability to ensure adequate organ perfusion during CPR and in the postresuscitation phase. In the early postresuscitation phase, vasopressin administration resulted in higher arterial blood pressure but a reversible depressant effect on myocardial function when compared with epinephrine; however, overall cardiovascular function was not irreversibly or critically impaired.

In patients with refractory cardiac arrest, intravenous vasopressin induced an increase in arterial blood pressure, and in some cases, ROSC, where standard therapy with chest compressions, ventilation, defibrillation, and epinephrine had failed. In a small (n = 40) prospective, randomized investigation of patients with out-of-hospital VF, a significantly larger proportion of patients treated with vasopressin were resuscitated successfully and survived 24 hours as compared with patients treated with epinephrine. Although this study lacked power, there was a nonsignificant trend towards an improvement in hospital discharge rate (P = .16) in the vasopressin group. In a large (n = 200) in-hospital CPR trial from Ottawa, Canada, comparable short-term survival was found in both groups treated with either vasopressin or epinephrine, indicating that these drugs may be equipotent when response times of rescuers are short.

After approximately 40 minutes of unsuccessful ACLS, 4 of 10 patients responded to vasopressin administration and had a mean increase in coronary perfusion pressure of 28 mm Hg. This is surprising, because an arterial blood pressure increase with any drug after such a long period of noneffective CPR management normally would not be expected. In this study, vasopressin caused an increase in coronary perfusion pressure and a decrease of epinephrine plasma levels, which is similar to an animal study with increased vital organ blood flow, but decreased catecholamine plasma levels after vasopressin.

Wenzel and Linder are currently coordinating a multicenter clinical study to determine the effects of 40 units vasopressin intravenously versus 1 mg epinephrine intravenously given up to two times in out-of-hospital cardiac arrest patients with VF, asystole, and PEA (unpublished data). This clinical trial is conducted under the aegis of the European Resuscitation Council and as of December 2000 had enrolled a total of 600 patients in 42 EMS systems (37 ground and 5 rotor-winged EMS programs) in Germany, Switzerland, and Austria. A preliminary analysis has revealed that the study is safe, randomization is working properly, no adverse results were reported, and that there is a good chance to find significant results after randomizing 1500 patients as planned. The new international
CPR guidelines of the AHA\textsuperscript{120} and European Resuscitation Council\textsuperscript{121} recommend 40 units vasopressin intravenously and 1 mg epinephrine intravenously as equally effective for the treatment of patients in VF. No recommendation was made to date for patients with asystole and PEA, and pediatrics because of lack of clinical data.

**CURRENT RECOMMENDATIONS**

In adult patients with VF, 40 units vasopressin or 1 mg epinephrine should be administered intravenously after failure of basic life support and defibrillation. Vasopressin is currently administered once, while epinephrine can be repeated every 2 to 5 minutes. The utility of higher dosages of epinephrine remains unclear despite the laboratory data supporting higher dosages.

There is limited experience with vasopressin in the setting of PEA or asystole, so epinephrine remains the pressor of choice empirically.\textsuperscript{122} Again, the optimal dosage remains unknown. Phenylephrine remains an attractive agent based on its pharmacology but clinical data supporting its use or optimal dosage are lacking.

Although there are no clinical data available, it is not unreasonable to consider combinations of vasopressin and catecholamines, and, in many clinical scenarios, the authors expect patients to receive 1 mg of epinephrine and, after failure to respond, to receive 40 units of vasopressin.

**THE FUTURE FOR PRESSOR DRUGS DURING CARDIOPULMONARY RESUSCITATION**

The ideal vasopressor for CPR is a drug that significantly increases myocardial and cerebral perfusion during CPR without increasing ischemic injury, and can be rapidly and titratably reversed in the immediate postresuscitation phase.\textsuperscript{123} Ultimately, the efficiency of these drugs will be judged with respect to their effect on long-term survival and neurologic outcome; however, determining the efficacy of any therapy given during CPR is extremely difficult because of confounding variables. Not only is there wide variability among patients with respect to potential responsiveness,\textsuperscript{124-125} but differences in health care systems may affect outcome because of variation in emergency medical services, response times, intensive care unit management, and access to diagnostic technology.\textsuperscript{126} In order to detect a significant increase in hospital discharge rates or neurological recovery, as many as 20,000 patients, several years, and millions of US dollars or euros might be necessary. For this reason, the primary endpoint of any reasonable study, such as the European vasopressor trial (anticipated number of patients = 1500) might be on the fraction of patients with ROSC or hospital admission. It is assumed that no individual agent will be found efficacious alone with respect to survival or neurological outcome. Only combinations of effective interventions may improve outcome enough to be detectable in reasonable clinical trials.

With respect to pressor drugs, combinations of agents may hold the greatest promise. Laboratory experience appears to be confirmed by observations in eight patients who were unsuccessfully resuscitated with epinephrine for approximately 10 to 20 minutes, subsequently received 40 units of vasopressin, and subsequently, all patients had ROSC, with three of eight patients being discharged alive from the hospital.\textsuperscript{127} This is not to say research in promising single agent therapies has ceased. Sun et al\textsuperscript{128} recently hypothesized that the $\alpha$-2 specific $\alpha$-methylnorepinephrine may take advantage of the pressors effects of $\alpha$-2 agonism while not inducing the postresuscitation myocardial dysfunction thought to caused in part by the nonspecific adrenergic effects of epinephrine. Using a rodent cardiopulmonary arrest model and comparing $\alpha$-methylnorepinephrine with epinephrine and placebo, the group concluded that $\alpha$-methylnorepinephrine was as effective as epinephrine for initial cardiac resuscitation but provided strikingly better postresuscitation myocardial function and survival.\textsuperscript{128} As these encouraging conclusions have yet to be verified in a human model, the ideal vasopressor and especially, the ideal dosing regimen for CPR in humans is yet to be proven. Although
combinations of drugs are theoretically attractive, development of a CPR cocktail will be difficult because of multiple potential permutations of different drugs and dosages. Experiments, for instance, have been performed with a combination of vasopressin, epinephrine, and nitroglycerin; however, determining optimal dose-response effects is difficult, and clinical experience is pending. Eventually clinicians may better understand the pressor activity necessary for optimizing hemodynamics and can design drugs that incorporate this without effects that exacerbate ischemic or reperfusion injury.

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