Treatment of Prolonged Ventricular Fibrillation
Immediate Countershock Versus High-Dose Epinephrine and CPR Preceding Countershock

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Background. Early countershock of ventricular fibrillation has been shown to improve immediate and long-term outcome of cardiac arrest. However, a number of investigations in the laboratory and in the clinical population indicate that immediate countershock of prolonged ventricular fibrillation most commonly is followed by asystole or a nonperfusing spontaneous cardiac rhythm, neither of which rarely respond to current therapy. The use of epinephrine in doses greater than those currently recommended has recently been shown to improve both cerebral and myocardial perfusion during cardiopulmonary resuscitation (CPR). The purpose of this study was to compare cardiac resuscitation outcome between immediate countershock of prolonged ventricular fibrillation with high-dose epinephrine therapy and conventional CPR before countershock of prolonged ventricular fibrillation in a canine model.

Methods and Results. After sedation, intubation, induction of anesthesia, and instrumentation, ventricular fibrillation was electrically induced in 28 dogs. After 7.5 minutes of ventricular fibrillation, animals were randomly allocated to two treatment groups: group 1, immediate countershock followed by recommended advanced cardiac life support (ACLS) interventions, or group 2, 0.08 mg/kg epinephrine and manual closed-chest CPR before countershock and ACLS. In both groups, ACLS was continued until a spontaneous perfusing rhythm was restored or for 20 minutes (total arrest time, 27.5 minutes). A spontaneous perfusing rhythm was restored in three of 14 group 1 animals and in nine of 14 group 2 animals ($p$=0.014 by sequential analysis method of Whitehead). Coronary perfusion pressure (aortic minus right atrial pressure during CPR diastole) before countershock was significantly greater in group 2 (21±7 mm Hg) when compared with mean circulatory pressure in group 1 (9±8, $p<0.01$).

Conclusions. The findings of this study suggest that a brief period of myocardial perfusion before countershock improves cardiac resuscitation outcome from prolonged ventricular fibrillation. (Circulation 1992;85:281–287)

Sudden unexpected cardiac death is most commonly due to ventricular fibrillation in patients with extensive atherosclerotic coronary artery disease.1,2 Immediate and effective treatment of ventricular fibrillation is the primary goal of advanced cardiac life support (ACLS). A number of clinical studies indicate that the earlier electrical defibrillation can be begun, the greater is the likelihood that countershock will be successful, ventricular fibrillation terminated, and survival improved from cardiac arrest due to ventricular fibrillation.3–5 Such studies support the early performance of electrical defibrillation by minimally trained first responders (e.g., emergency medical technicians) using conventional transthoracic countershock techniques or automated electrical defibrillation technology.6,7

Successful electrical defibrillation can be defined as 1) termination of ventricular fibrillation, or 2) termination of ventricular fibrillation followed by a spontaneous perfusing cardiac rhythm. Although countershock may be successful in terminating ventricular fibrillation, these definitions have different clinical implications. It has been shown that immediate countershock of prolonged ventricular fibrillation is most often followed by asystole, or an electrocardiogram (ECG) rhythm not associated with arterial
pressure pulses (broadly defined as electromechanical dissociation, or EMD). Such an outcome has been reported after one or more countershocks in up to 60% of patients with sudden cardiac death caused by ventricular fibrillation and is almost always fatal.8-10 The mechanism for postcountershock asystole or pulseless rhythms is unknown but may be related to the duration of global myocardial ischemia, the limited coronary blood flow produced by closed-chest CPR, or the effects of repeated countershocks on myocardial ultrastructure.11-13 Of note, immediate countershock of prolonged ventricular fibrillation has been used as an animal study model for EMD.14-16

The likelihood of successful restoration of spontaneous circulation after electrical countershock appears to be time dependent. The earlier that countershock can be performed, the greater the likelihood that defibrillation will be followed by a spontaneous perfusing rhythm and survival.4 As the duration of ventricular fibrillation is prolonged and immediate countershock is used as first therapy, the likelihood of successful cardiac resuscitation (i.e., return of a spontaneous cardiac rhythm and systemic perfusion) decreases due to the increasing occurrence of postcountershock asystole and EMD.

Epinephrine use during cardiac arrest and CPR has been shown to increase both myocardial and cerebral perfusion by increasing arterial tone and improving the arteriovenous perfusion gradients necessary for myocardial and cerebral blood flow.17,18 The magnitude of the coronary perfusion gradient and myocardial blood flow has been shown to correlate with successful resuscitation.17,19 The effects of epinephrine on cerebral and myocardial perfusion during cardiac arrest and CPR have been shown to be dose dependent.20,21 An increasing number of experimental and clinical studies support the use of high-dose epinephrine as a means to improve systemic perfusion during prolonged ventricular fibrillation and closed-chest CPR.22

Although early countershock of ventricular fibrillation is recommended, immediate countershock of prolonged ventricular fibrillation most often results in asystole or EMD. The effect of high-dose epinephrine combined with CPR before countershock on such an outcome has not been evaluated. The purpose of this study was to compare cardiac resuscitation outcome between immediate countershock of prolonged ventricular fibrillation with high-dose epinephrine therapy and conventional CPR preceding countershock of prolonged ventricular fibrillation in a canine model of cardiac arrest.

Methods

This study was approved by the animal resource center of our institution and conforms to the position of the American Heart Association on research animal use.

Twenty-eight mongrel dogs of either sex weighing 20–30 kg were fasted overnight but allowed ad libitum access to water. Anesthesia was induced with thiopental (10–20 mg i.v., titrated to effect) and orotracheal intubation was performed. Anesthesia was maintained with halothane, 0.5–1.0%, and a mixture of nitrous oxide and oxygen (60:40 ratio). During instrumentation and the control period, animals were mechanically ventilated and minute ventilation was adjusted to maintain an arterial pH of 7.38–7.42 and an arterial PaCO2 of 30–40 mm Hg. Core body temperature, measured in the pulmonary artery, was determined during the control period and was never less than 37° during the control or cardiac arrest and resuscitation study intervals.

After a surgical plane of anesthesia was attained, calibrated micromanometer-tipped catheters (Millar Instruments, Houston, Tex.) were inserted into the femoral arteries and veins. A multilumen, thermodilution cardiac output catheter (American Edwards Laboratories, Anasco, Puerto Rico) was positioned in a branch of the pulmonary artery. Catheter tips were advanced into the ascending aorta, right atrium, and pulmonary artery. The right external jugular vein was then surgically exposed and a bipolar pacing catheter was inserted and advanced into the right ventricle. Catheter tip positions were confirmed by fluoroscopy and by characteristic pressure traces. Standard lead II of the surface ECG was monitored continuously. Volume expansion with intravenous fluid administration before induction of ventricular fibrillation was not used.

After instrumentation, animals were randomly assigned to one of two treatment groups. Group 1 animals were immediately countershocked after prolonged ventricular fibrillation and served as the control group. Group 2 animals were initially treated with high-dose epinephrine (0.08 mg/kg) followed by closed-chest CPR for 3–5 minutes before electrical countershock.

Before randomization and induction of cardiac arrest, the following control variables were measured: 1) systolic, diastolic, and mean aortic pressures, 2) mean right atrial pressure, 3) thermodilution cardiac output (determined in triplicate) (American Edwards Laboratories Cardiac Output Computer), and 4) arterial PaO2, PaCO2, and pH (Radiometer ABL 3, Copenhagen). Hemodynamic data were recorded by using a multichannel physiological Recorder (Electronics for Medicine VR-12, Pleasantville, N.Y.).

Ventricular fibrillation was induced electrically by passing AC current via the bipolar electrode catheter positioned in the right ventricle. Ventricular fibrillation was confirmed by the surface ECG recording and the characteristic decline in intravascular pressures.

After 7.5 minutes of ventricular fibrillation without artificial circulatory or ventilatory support, electrical countershock was immediately attempted in group 1 animals. This time interval between onset of ventricular fibrillation and initial defibrillation attempts approximates clinical experience.23 The first shock delivered 100 J (approximately 4 J/kg). If ventricular fibrillation persisted, a second countershock at 100 J...
was immediately performed followed by 200 J (approximately 8 J/kg). If countershocks were followed by persistent ventricular fibrillation, asystole, or EMD, closed-chest CPR was begun. The animal was placed in the left lateral decubitus position and the thorax was manually compressed at a rate of 80–100 compressions per minute with a compression/relaxation ratio of approximately 50%. Positive-pressure ventilations were performed with a bag-valve device at a compression/ventilation ratio of 8:1 using a supplemental oxygen flow rate of >15 l/min. Epinephrine, 0.04 mg/kg of a 1:10,000 solution, was immediately administered via a central venous injection (right atrial port of a multilumen catheter). This dose was repeated at 5-minute intervals if indicated and in accordance with current ACLS guidelines.

After 7.5 minutes of unsupported ventricular fibrillation, group 2 animals were immediately treated with 0.08 mg/kg of a 1:10,000 epinephrine solution administered via a central venous injection (right atrial port of multilumen catheter). Closed-chest CPR was then immediately performed as for group 1 animals. After approximately 5 minutes of CPR, closed-chest CPR and countershocks were administered sequentially as described for group 1 animals. Additional doses of epinephrine, 0.08 mg/kg, were administered at 5-minute intervals if indicated and in accordance with current ACLS guidelines for the management of cardiac arrest rhythms.

For group 1 and group 2 animals in which the first three sequential countershocks were not followed by a spontaneous cardiac rhythm associated with arterial pressure pulses of >50 mm Hg, closed-chest CPR, pharmacological support, and repeated countershocks, in accordance with current guidelines, were provided for up to an additional 20 minutes from the first countershock (total arrest time, 27.5 minutes). Drug therapy included lidocaine, procainamide, atropine, or dopamine as indicated. All drugs were administered via the central venous route and additional countershocks (8 J/kg) were given as necessary. For the purposes of this study, successful cardiac resuscitation was defined as arterial pressure pulse of >50 mm Hg sustained for 30 minutes. Successfully resuscitated animals were observed for an additional 30 minutes.

During arrest and CPR, the following variables were measured at 5-minute intervals in all animals: 1) peak systolic aortic and right atrial pressures (compression phase of CPR), 2) diastolic aortic and right atrial pressures (relaxation phase of CPR), 3) CPR coronary perfusion pressure (CPP) (maximum diastolic aortic–right atrial pressure difference), and 4) arterial PaO₂, PaCO₂, and pH.

**Statistical Methods**

The end point of this study, successful cardiac resuscitation, was designed to be analyzed using the sequential method of Whitehead. This form of analysis allows a reduction in the expected sample size for a trial while yielding well-defined risks for both type I and type II errors. The study was designed to have a statistical power of 0.95 to detect an increase in survival from 0.2 (group 1) to 0.6 (group 2). The log-odds ratio was used as the measure of treatment efficacy. Data were analyzed after the outcomes from 12, 20, and 28 animals were known. The values of two statistics, V and Z, were calculated at each analysis. The statistic Z is a measure of the degree to which survival in group 2 (the treatment group) is better than in the control group (group 1). The statistic V is a measure of the amount of information contained in the data. These values of V and Z were then plotted with V on the horizontal axis and Z on the vertical axis.

In this form of sequential analysis, subjects are tested and the accumulating data are analyzed and plotted until the point determined by the last values of V and Z fall outside one of two boundaries. If the plot crosses the lower boundary, the treatment or study group (group 2 in this study) is no better than the control group (group 1 animals in this study) with a defined type II (β) error of <0.05. If the plot crosses the upper boundary, the treatment group is more efficacious than the control group, with a probability value of <0.05.

Interval data are presented as mean±SD. Differences in control values and those recorded during CPR between group 1 and group 2 animals were compared using the unpaired, two-tailed t test applied to equal sample sizes. In resuscitated animals, control and postarrest variables were compared using the paired, two-tailed t test. χ² was used to assess differences in rhythm outcomes between group 1 and group 2. A probability value of <0.05 was considered statistically significant.

**Results**

Control values for group 1 and group 2 animals are shown in Table 1. There were no statistical differences in measured prearrest variables.

Group 1 animals were immediately countershocked one to three times after 7.5 minutes of ventricular fibrillation. Initial postcountershock rhythms after up to three electrical defibrillation attempts and outcome after an additional 20 minutes of advanced life support are shown in Tables 2 and 3.
TABLE 2. Initial Postcountershock Rhythm

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asystole</td>
<td>10*</td>
<td>3</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Sinus</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

*p<0.01 vs. group 2.

The most common outcome was postcountershock asystole, and only three of 14 animals could be resuscitated.

Group 2 animals were given 2 mg epinephrine (approximately 0.08 mg/kg) and received conventional closed-chest CPR before countershock. The coronary perfusion pressure (diastolic aortic minus diastolic right atrial pressure measured during the relaxation phase of CPR) averaged 21±7 mm Hg before the first countershock in group 2 animals. Initial postcountershock rhythms after up to three electrical defibrillation attempts and outcome after an additional 20 minutes of advanced life support are shown in Tables 2 and 3. Countershock after epinephrine and CPR resulted in a sinus rhythm in three group 2 animals or persistent ventricular fibrillation that usually responded to additional countershocks and drug therapy. Time to resuscitation and total number of countershocks are summarized in Table 3. Group 2 animals received as many countershocks as group 1 animals, and time to restoration of spontaneous cardiac activity was not significantly different in either group resuscitated.

As shown in Figure 1, the trial was terminated after 28 animals were randomly allocated to the control (group 1) or the study group (group 2). Three of the 14 dogs (21%) assigned to group 1 were successfully resuscitated and nine of 14 dogs (64%) assigned to group 2 were successfully resuscitated (Table 2). Analysis of this termination point was performed using Whitehead's method, and yielded a probability value and an unbiased estimate of treatment efficacy. The average inspection interval, which is average change in V between inspections, was equal to 0.57. The probability value for the trial was 0.014 and the 95% confidence interval for the true treatment efficacy (group 2), using the log-odds ratio, was 0.20–3.29. Assuming a survival rate of 20% in the control group (group 1), these limits correspond to a resuscitation rate of 23–87% in the treatment group (group 2). The median unbiased estimate of treatment efficacy was 1.76. Assuming a cardiac resuscitation rate in the control group of 20%, this would correspond to a resuscitation rate in the treatment group of 59%.

Discussion

The findings of this study indicate that immediate countershock of prolonged ventricular fibrillation in the absence of artificial circulatory or ventilatory support (CPR) most often results in postcounter-shock asystole or persistent ventricular fibrillation. Early countershock of ventricular fibrillation of short duration is the intended goal of prehospital ACLS. However, a number of published studies suggest that victims of prehospital sudden cardiac death caused by ventricular fibrillation will not benefit from such an intervention when used immediately as the first intervention in the late management of prolonged ventricular fibrillation and support the observations of outcomes in our study model.8–10,28 The success of immediate countershock of ventricular fibrillation appears to be time dependent, and return of effective circulation after immediate countershock of prolonged ventricular fibrillation in the absence of CPR is uncommon.

This study was specifically designed to replicate clinical experience with the treatment of prehospital sudden cardiac death caused by ventricular fibrillation. The majority of victims of prehospital sudden cardiac death caused by ventricular fibrillation are not afforded electrical defibrillation until after 7–8 minutes of cardiac arrest; an even greater minority

![Figure 1](http://circ.ahajournals.org/)

FIGURE 1. Results of the trial presented graphically. Points determined by observed values V and Z are plotted after every group of four dogs; data were analyzed and considered for termination of the study only after outcomes of 12, 20, and 28 canines were available. These points are represented with solid circles. Terminal values of V and Z used to calculate probability value (0.014) and 95% confidence limits were 1.714 and 3.000, respectively. A terminal value falling below the lower line would indicate that treatment group outcome was not better than the control group; terminal value falling above the upper line indicates that treatment group outcome was better than that of the control group.
receive early CPR by lay citizens before defibrillation attempts.23

Only 21% of animals treated with immediate countershock after prolonged ventricular fibrillation were successfully resuscitated (i.e., a spontaneous perfusing rhythm was restored). In the clinical setting, resuscitation rate (return of spontaneous circulation and hospital discharge) from out-of-hospital cardiac arrest caused by ventricular fibrillation averages 20% over a wide range of clinical populations when electrical defibrillation is the first intervention.23 The observed postcountershock rhythms in this animal study are comparable with those reported in clinical studies.8–10 Immediate countershock of prolonged ventricular fibrillation most often resulted in asystole. In clinical studies, a wide QRS complex rhythm not associated with arterial pulsations (EMD) or persistent ventricular fibrillation are often reported.

Epinephrine has been shown to increase both cerebral and myocardial perfusion during prolonged cardiac arrest and closed-chest CPR.17,18 More recently, the beneficial effects of epinephrine, when administered during cardiac arrest and closed-chest CPR, have been shown to be dose dependent.20,21 Doses of epinephrine greater than those currently recommended have been shown to increase the likelihood of successful defibrillation after prolonged cardiac arrest caused by ventricular fibrillation.17 In this study, we have demonstrated its beneficial effects in a clinically relevant animal model of prolonged ventricular fibrillation in a dose that exceeds those currently recommended (approximately 0.01 mg/kg) but far less than those demonstrated to be optimal in other animal models (0.08 mg/kg versus 0.1 or 0.2 mg/kg)22 or in limited clinical reports.29,30

In this study, specific statistical methods were used to yield the greatest statistical power. The sequential analysis method was used and is well described as a method to simultaneously minimize sample size and the risks of α and β error. The use of high-dose epinephrine and closed-chest CPR before electrical countershock of prolonged ventricular fibrillation significantly improved short-term resuscitation outcome when compared with immediate countershock (64% versus 21%, p=0.014).

The mechanism by which precountershock treatment with high-dose epinephrine and CPR improved cardiac resuscitation outcome in this study is most probably related to its effects on myocardial blood flow. Epinephrine combined with chest compressions significantly improved the well described CPR myocardial perfusion gradient (aortic minus right atrial pressure difference measured during the chest relaxation phase of closed-chest CPR) before countershock via its well described α-adrenergic effects.31 This easily measured perfusion gradient has been well correlated with myocardial blood measured with radiolabeled microsphere methods during prolonged cardiac arrest and closed-chest CPR after induced ventricular fibrillation in a number of animal species and in a number of cardiac arrest models.17,18,21,32 In this study, all animals who attained a CPR coronary perfusion pressure of >20 mm Hg, regardless of study group allocation, were successfully resuscitated to a spontaneous perfusing rhythm. This was more commonly observed in animals pretreated with epinephrine and closed-chest CPR before attempted countershock of prolonged ventricular fibrillation.

The β1-adrenergic effects of epinephrine may also have contributed to the improved outcome observed in the treatment group. A number of previous studies have directly or indirectly addressed the importance of epinephrine’s β-adrenergic effects during cardiac arrest. In an asphyxial cardiac arrest model, the β-adrenergic stimulating properties of epinephrine were felt to be inconsequential for successful resuscitation.33,34 Such a conclusion was based on outcome studies in animals subjected to nonelective β-blockade in a model of cardiac arrest infrequently encountered in clinical practice. It has also been suggested that epinephrine therapy may worsen the myocardial supply/demand imbalance during ventricular fibrillation and artificial circulatory support.35,36 However, the latter concern is not supported by recent studies in which higher doses of epinephrine were used and compared with pure α-agonists.37–39 High-dose epinephrine improved global myocardial oxygen extraction and did not selectively affect the ratio of subendocardial to subepicardial myocardial blood flow. In two studies comparing epinephrine with pure α-agonists, successful defibrillation, defined as a mean arterial pressure >60 mm Hg and a narrow QRS complex (<120 msec) for 1 minute, was more commonly encountered in animals treated with epinephrine.37,38 However, successful defibrillation data did not attain statistical significance because of the small sample size. Two studies suggest that epinephrine therapy before countershock may not improve the likelihood of termination of ventricular fibrillation but may increase the frequency of a return to a spontaneous perfusing rhythm.40,41 Such an outcome may be the result of β1-adrenergic stimulation after prolonged myocardial ischemia.

Only one previous study has assessed differences in outcome between immediate countershock of prolonged ventricular fibrillation and precountershock treatment with one or more drugs or other ACLS interventions provided by prehospital rescuers with advanced training.10 Precountershock treatment appeared to offer no advantage over immediate countershock. However, the findings of this clinical study were based on a retrospective review of available records, treatment groups were not randomized, the study population was not well defined, and precountershock treatment is never described. The overwhelming majority of patients allocated to “sweetening up” before countershock in the Martin study were unwitnessed cardiac arrests in which the first documented rhythm was described as ventricular fibrillation. Available data indicate that such patients are unlikely to benefit from any intervention.
The limitations of this study, as related to the study purpose or hypothesis, include the following: 1) a single dose of high-dose epinephrine was used, 2) a single duration of ventricular fibrillation before study interventions were begun, 3) use of high-dose epinephrine and CPR after immediate countershock in animals subjected to prolonged ventricular fibrillation was not evaluated, 4) the value of CPR alone before countershock was not studied, and 5) the selected resuscitation end point (i.e., a spontaneous perfusing rhythm maintained for 30 minutes) does not represent long-term survival.

The optimum dose of epinephrine, based on a milligram per kilogram dose, has yet to be defined. The dose used in this study (0.08 mg/kg) is greater than those currently recommended but substantially less than those reported to be optimal (0.2 mg/kg). The interval between onset of cardiac arrest caused by ventricular fibrillation and definitive intervention was selected based on an average of reported clinical experience in a wide clinical population. Outcome may have been different if shorter or longer intervals had been studied. The value of high-dose epinephrine after immediate conventional therapy has not been determined but is being evaluated in multicenter studies. An alternative method to evaluate the benefit of high-dose epinephrine and CPR before countershock would be to give the same dose of epinephrine to different study groups randomized to epinephrine/CPR before countershock or countershock followed by epinephrine/CPR. This alternative study design was not incorporated in the current study. A number of laboratory studies indicate that CPR alone after prolonged ventricular fibrillation is unlikely to be effective in restoring a spontaneous rhythm and effective circulation when used as the only intervention before countershock of prolonged ventricular fibrillation. In this study, only short-term cardiac resuscitation outcome was evaluated but exceeds that reported by other laboratories.

In this animal study, we have attempted to replicate clinical experience in the management and outcome of out-of-hospital sudden cardiac death. In the majority of the clinical population, sudden death is not witnessed, citizen or bystander basic CPR is not provided, and early electrical defibrillation is not available. In this study, the outcome of control animals closely approximates clinical experience. The precountershock use of epinephrine and closed-chest CPR significantly improved cardiac resuscitation outcome. The observed difference in outcome may be due to improved myocardial perfusion before countershock as well as the $\beta_1$-adrenergic effects of epinephrine. Although early countershock of ventricular fibrillation of short duration has been shown to result in improved outcome, immediate countershock of prolonged ventricular fibrillation may prevent successful cardiac resuscitation.

References


KEY WORDS • catecholamines • cardiopulmonary resuscitation • cardiac arrest
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