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Endotracheal Versus Intravenous Epinephrine During Electromechanical Dissociation with CPR in Dogs

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ABSTRACT

The dose-response curves of epinephrine given either IV or endotracheally (ET) were compared during resuscitation from electromechanical dissociation (EMD). Ten anesthetized dogs were subjected to a two-minute period of electrically induced ventricular fibrillation (VF) followed by defibrillation without CPR to produce EMD. Mechanical CPR was followed by injection of either ET or IV epinephrine. Successful response was defined as a return of pulsatile blood pressure within two minutes of drug administration. Using log-dose increments of epinephrine, experimental trials were repeated in each animal. The IV and ET median effective doses were 14 and 130 $\mu\text{g}/\text{kg}$, respectively. When the trials were successful, the time between drug administration and either arterial blood pressure increases or return of spontaneous circulation did not differ significantly for the ET and IV groups. These results show that the dosage for epinephrine delivered ET must be higher than the IV dosage to achieve the same response during CPR.

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Key words: electromechanical dissociation, epinephrine, experimental; epinephrine, experimental, EMD, methods

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INTRODUCTION

Epinephrine has been the most thoroughly evaluated drug used in advanced cardiac life support. A succession of studies, beginning with Crile in 1906,¹ have shown repeatedly that when epinephrine is added to resuscitation procedures following cardiac arrest, the victim's chances of survival are improved significantly. Redding's work in the 1960s established that the value of epinephrine lies principally in its alpha agonist activity, which produces peripheral vasoconstriction, increased blood pressure, and improved myocardial perfusion.²⁻⁵ The mechanism was confirmed by subsequent research studies.⁶⁻⁸

Because the IV route of drug delivery may be difficult and time consuming during periods of circulatory arrest, the American Heart Association (AHA) currently recommends that epinephrine also be given through the endotracheal tube.⁹ Established protocol requires that epinephrine be given in 0.5-mg to 1-mg doses IV and repeated at five-minute intervals until the circulation is restored. Based on Greenberg's studies in animals with normally beating hearts,^{10,11} the AHA recommends that 1 mg epinephrine diluted in a 10-mL solution be given through the endotracheal tube as an alternative to the IV route. Pilot studies in our laboratory revealed difficulties in eliciting blood pressure responses using the recommended protocol for tracheobronchial epinephrine administration.⁸ In these pilot studies, three anesthetized dogs were subjected to electrically induced ventricular fibrillation (VF), and CPR was started immediately. We observed no change in blood pressure following injection of endotracheal epinephrine (0.1 mg/kg); however, deep intrapulmonary epinephrine* (0.1 mg/kg) increased the blood pressure within a few seconds. In addition the blood pressure did not increase following either tracheal or deep bronchial injection of epinephrine in the currently recommended doses. These observations led us to speculate that during the low-blood-flow state that exists during CPR, epinephrine is not absorbed readily through the conducting airways, and that the currently recommended dosage may be too low to be effective. We therefore undertook a study to compare the effectiveness of various doses of epinephrine given IV or endotracheally (ET) during CPR.

METHODS

Animal Preparation

Ten mongrel dogs of either sex weighing 13 kg to 29 kg (mean, 22.6 kg) were anesthetized with IV pentobarbital sodium (30 mg/kg) and intubated with a cuffed endotracheal tube. Intravascular catheters were placed to monitor pressures in the right atrium, aortic arch, and left ventricle. The animals were heparinized (1 mg/kg) to retard intravascular coagulation at the catheter tips. Physiologic monitoring was done on a Physiograph recorder (Narco Bio-systems, Houston, Texas). Four channels of data were recorded -- ECG lead II, aortic arch pressure, central venous pressure, and left ventricular pressure.

* This technique requires a longer catheter to deposit drug much deeper into the lung substance, compared to the endotracheal route.

Experimental Protocol

The animal model used in our study was developed previously by Thijs and associates¹² and reproduced in studies by other investigators.^{13,14} The model was designed to simulate clinical situations in which defibrillation occurs without adequate coronary perfusion, producing EMD. VF was induced electrically using five- to ten-volt, 60-Hz electric pulses applied to the left ventricular catheter, which contained a 0.1-mm stainless steel wire within the lumen to carry current to the heart. After two minutes of VF, a defibrillation countershock was applied and repeated if necessary until cardiac electrical activity resumed. During the next 30 seconds, EMD was confirmed by observing the ECG and pressure channels to be certain that electrical activity remained without evidence of any blood pressure pulses.

At this point, standard CPR was initiated using a mechanical Thumper[®] (Michigan Instruments, Grand Rapids, Michigan) to provide chest compressions and ventilation. After pressures were stabilized the test drug was administered and CPR was continued. CPR was discontinued as soon as the graphic record showed evidence of returning pulsatile blood pressure or a maximum of two minutes after drug administration. Animals that were able to maintain their own circulation at this time were termed successes, and those that required further help were termed failures. Additional measures were used to resuscitate the latter group so that further experimental trials could be performed. These measures included increasing the chest compression force to improve CPR and/or giving intracardiac epinephrine. This experimental procedure (Figure 1) was repeated using logarithmically incremental epinephrine doses until the animal no longer could maintain a diastolic arterial pressure of 100 mm Hg.

Time intervals were interspersed between trials to allow for drug metabolism and animal recovery. Following IV dosing the recovery period was 30 minutes, or more than five half-lives of epinephrine. In the absence of pharmacokinetic studies for this endotracheal model, the recovery period was one hour, or approximately three times longer than the time required for blood pressure recovery to pre-fibrillation levels.

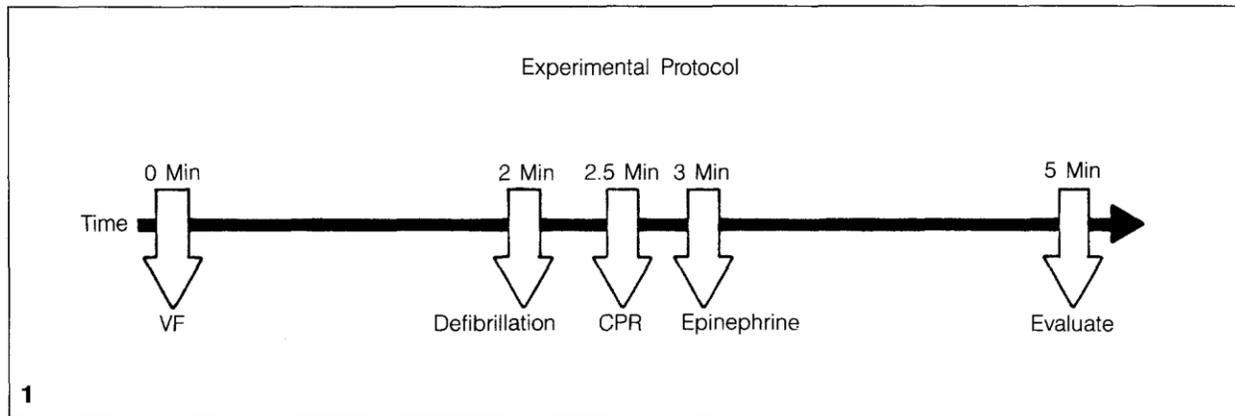


Fig. 1. Diagrammatic representation of protocol for each experimental trial.

In order to evaluate the effectiveness of epinephrine, it is important to select an animal model in which CPR alone is unable to restore the circulation successfully. Therefore, in the first experimental trial each animal received saline as the test drug, and the chest compression force was adjusted to produce a diastolic pressure of approximately 20 mm Hg. The experiment continued only after failure to resuscitate within two minutes was confirmed using CPR and saline. The arterial blood pressures achieved during this trial were maintained throughout subsequent trials.

Drug Administration Techniques

Following an experimental trial using saline as the test drug, epinephrine was given as a bolus either IV or ET, and the route was alternated in subsequent experimental trials. In half the dogs the IV route was used first, and in the other half the ET route was used first. The initial drug dosage for each route (10 $\mu\text{g}/\text{kg}$ IV or 100 $\mu\text{g}/\text{kg}$ diluted in 10 mL saline ET) was selected to have a reasonable chance of success based on prior observations in other animals. Subsequent drug dosage was based on the outcome from the first experimental trial. When the initial dose was effective in restoring the circulation, a lower dose was then given; if ineffective, a higher dose was used.

ET drug delivery was accomplished using a 13-F, 50-cm-long catheter equipped with a spray nozzle on the distal tip (experimental model, Cook Inc, Bloomington, Indiana). The catheter, which produced a fine mist spray, was advanced to a position within the trachea approximately three inches distal to the end of the ET tube. The drug was sprayed quickly into the trachea, followed by air injection to clear the catheter. Then two to three full, maximal ventilations were blown into the endotracheal tube to aid in distributing the drug into the deeper airways, and CPR as resumed.

Data Analysis

A cumulative frequency distribution was constructed using successful resuscitations within two minutes as the end response for each drug dose administered. In constructing these curves it was assumed that if success had been achieved with dose, X, in a given animal, then success also would have been achieved with doses larger than X in that animal, even though all larger doses may not have been tested in that animal. This analytical approach is similar to that described by Goldstein and associates for constructing dose-response curves from the distribution of drug sensitivities.¹⁵ The median effective dose (ED₅₀) was derived following Probit transformation of the cumulative frequency distribution data.¹⁶

To determine further the effects of epinephrine dosage, additional variables were assessed when the resuscitation trials were successful. These variables included the time from drug delivery to evidence of initial blood pressure response, the time from drug delivery to return of spontaneous circulation, the post-resuscitation peak arterial systolic and peak diastolic pressures, and the duration of hypertension. The methods used in measuring each of these parameters are shown (Figure 2).

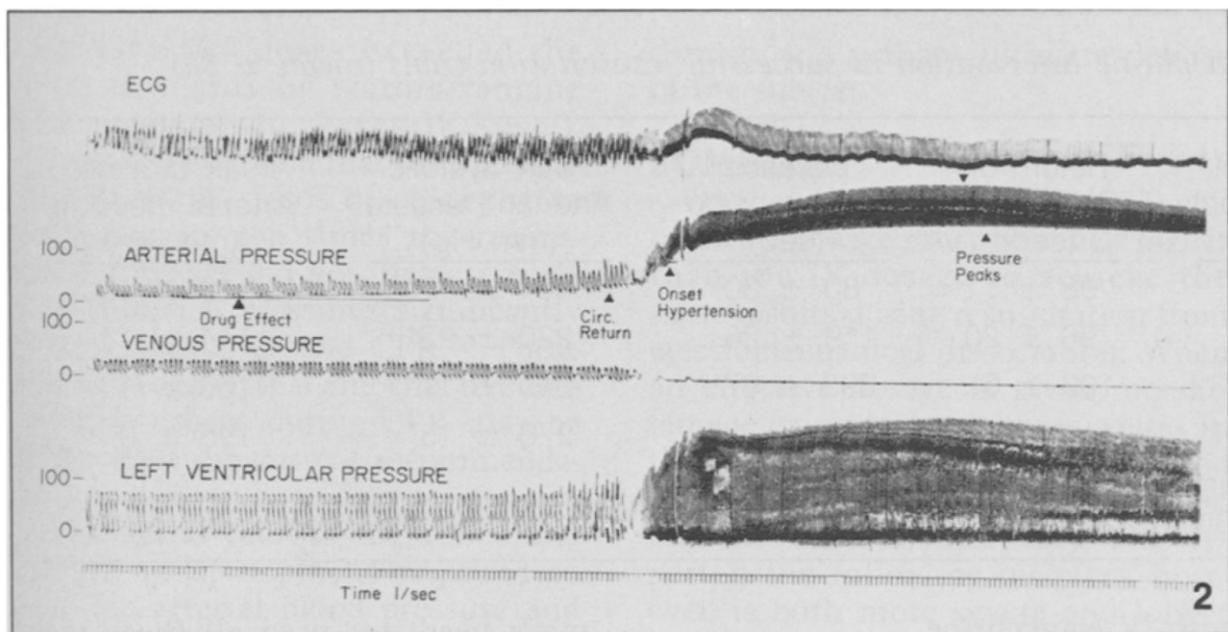


Fig. 2. Physiologic tracing from a dog following epinephrine injection during CPR. Illustrations include onset of arterial blood pressure response, onset of returning pulsatile blood pressure, onset of hypertensive episode, and peak systolic and diastolic arterial pressures.

The initial blood pressure response following drug administration was defined by the intersection of two lines drawn at the base of the control CPR pressures and at the base of the rising pressure slope (Figure 2). The return of spontaneous circulation was coincident with blood pressure pulses superimposed on the Thumper[®]-generated pulses. The duration of hypertension included the time period when the blood pressure exceeded 140/80 mm Hg. An ANOVA was performed on these data to test the null hypothesis that population means were equal within the groups using the $P < 0.05$ level of significance.

RESULTS

In the ten animals epinephrine was given in 21 IV doses and 19 ET doses. Ten IV and nine ET epinephrine doses were successful in promoting a return of spontaneous circulation. The relationships between epinephrine concentration and the cumulative percentage of successful resuscitations are shown (Figure 3). Epinephrine given by the ET route required doses that were approximately ten times higher than the epinephrine doses required for the IV route. The IV and ET median effective doses (ED50) were 14 $\mu\text{g}/\text{kg}$ and 130 $\mu\text{g}/\text{kg}$, respectively.

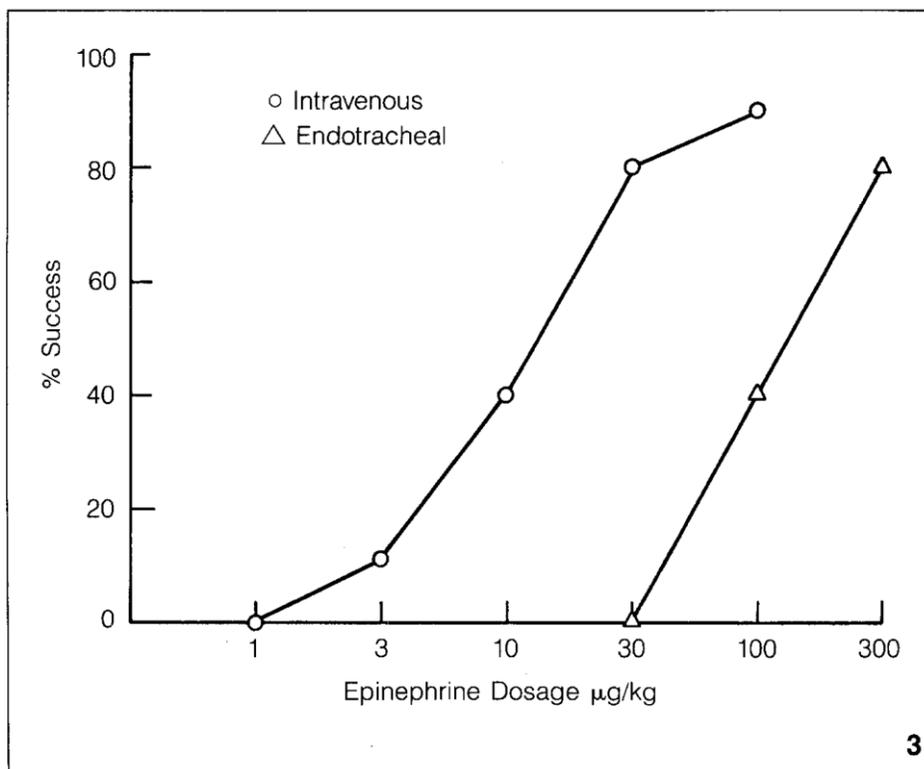


Fig. 3. Cumulative dose-response relationships for recovery of animals following injection of epinephrine either IV or ET.

Blood pressures were assessed during the short period of CPR just prior to the administration of epinephrine. Aortic diastolic pressures for the IV and ET groups were 19.9 ± 1.02 mm Hg and 18.53 ± 0.65 mm Hg (mean \pm SE), respectively. The pre-drug coronary perfusion pressures (aortic pressure minus right atrial pressure) were 7.62 ± 0.6 mm Hg for the IV trials and 7.78 ± 0.65 mm Hg for the ET trials. These baseline pressures did not vary significantly between IV and ET groups.

Evidence for early epinephrine effect was assessed by measuring the onset of blood pressure rise and the initial evidence of spontaneous pulsatile blood pressure. There were no significant differences between the IV and ET groups (Table) in either of these parameters. To determine the action of epinephrine in the immediate post-recovery period, the peak arterial pressures and the duration of the hypertensive episode were measured. Both systolic and diastolic arterial blood pressures achieved were significantly higher following the higher-dose ET epinephrine injections, compared with the lower doses given IV (Table). In addition the hypertensive event lasted significantly longer following ET injection compared with IV injection of epinephrine.

TABLE. Variables following epinephrine intervention in successful resuscitation trials (mean \pm SE)

Route	Dose (μ g/kg)	Onset of Drug Effect (sec)	Return of Circulation (sec)	Duration Hypertension (sec)	Peak Systolic Arterial Pressure (mm Hg)	Peak Diastolic Arterial Pressure (mm Hg)
Intravenous	10	50 \pm 8	98 \pm 11	80 \pm 30	164 \pm 12	119 \pm 13
Intravenous	30	36 \pm 9	96 \pm 20	119 \pm 26	220 \pm 22*	144 \pm 18
Endotracheal	100	45 \pm 13	103 \pm 6	393 \pm 97*†	240 \pm 11*	166 \pm 13
Endotracheal	300	49 \pm 11	114 \pm 12	500 \pm 28*†	278 \pm 13*	195 \pm 9*

*Group significantly different from 10 μ g/kg group ($P \leq .05$).

†Group significantly different from 30 μ g/kg group ($P \leq .05$).

DISCUSSION

The results of our study indicate that epinephrine must be given in a much higher dosage by the ET route compared with the central venous route in order to restore circulation following cardiac arrest associated with EMD. These results are consistent with studies by Roberts and coworkers,¹⁰ who demonstrated blood levels of epinephrine to be ten times lower with ET epinephrine compared with IV epinephrine. These findings suggest that the higher dose requirement for the ET drug during CPR reflects the amount of drug actually absorbed into the circulation by the pulmonary capillary bed. The ET-injected drug presumably remains partially in the conducting airways, where it is poorly absorbed, particularly during the low-blood-flow state associated with CPR. The result is an inadequate delivery of drug to the deep absorbent surfaces of the alveolar membranes.

Evidence for this drug pool in the airways has been described in studies by Elam¹⁷ and Roberts.^{10,11} Elam and coworkers described a prolonged drug effect following ET administration that they attributed to a "depot" of drug that produced an IV drip effect delivering small

increments of drug over a fairly long period. Roberts and colleagues also found that ET epinephrine significantly prolonged both the pharmacological effects and the epinephrine blood levels compared with IV administration.

Techniques aimed at dispersing the drug more quickly into the lower airways have been developed in the laboratory. Elam raised the animal's head 30 degrees and used a long catheter that he moved back and forth to disperse the drug over the bronchial surfaces.¹⁷ Redding¹⁸ found undiluted epinephrine (1 mg in 1 mL solution) given ET to be unsuccessful during resuscitation. By diluting epinephrine in 10 mL saline or water, however, greater absorption occurred, resulting in resuscitation successes equal to those of IV or intracardiac delivery. Greenberg and Spivey¹⁹ demonstrated the importance of forceful ventilations to maximize the distribution of drug into the deeper lung surfaces. With the exception of raising the animals head, we used all these techniques to maximize drug dispersion. In addition the catheter chosen for these experiments was one capable of producing a finer spray than other currently available products. By optimizing ET delivery we hoped to produce the optimal dose-response to epinephrine. The ET route, however, still required epinephrine doses ten times higher than the IV route to effect successful resuscitation.

The effectiveness of epinephrine also has been related to the timing of its delivery during the resuscitation procedure. Redding noted that epinephrine responsiveness decreased when drug delivery was delayed following cardiac arrest, resulting in fewer successful resuscitations.⁵ The site for drug injection during CPR may play a crucial role in aiding early delivery. Previous studies reported a more rapid onset of epinephrine effects following ET injection compared with femoral IV injection.¹⁷ By bypassing a sluggish circulation, the ET route provided a shorter pathway to the peripheral vasculature. In our study the onset of drug effects following ET delivery compared favorably with the central IV route. These findings indicate that a portion of the large ET bolus is absorbed immediately into the circulatory system.

Establishing an effective epinephrine dosage during CPR is a worthwhile yet difficult problem. Currently the AHA recommends giving 0.5 to 1 mg (equivalent to 7.5 µg/kg to 15 µg/kg in a 70-kg man) epinephrine IV or 1 mg ET.⁹ In our study, epinephrine dosages required to bring about successful recovery of the circulation greatly exceeded the current recommendations. Four of the successful IV doses were double the recommended human value; the nine successful ET doses exceeded the AHA standards by factors ranging from seven to 40. Recently Kosnik and coworkers found that centrally administered IV doses of epinephrine ranging up to ten times the recommended dosage did not increase coronary perfusion pressures significantly in dogs during VF and CPR.²⁰ These findings suggest that the effective epinephrine dosage during CPR may be higher than the current recommendations.

Additional factors influence the amount of epinephrine required to raise the arterial blood pressure and restore the circulation. For example, the amount of blood flow generated by CPR and the individual's responsiveness to epinephrine are two such factors. To minimize the effects of these factors, our study compared dose-responses to ET and IV epinephrine in the same animal using CPR that was standardized to produce comparable blood pressures during each trial. The effectiveness of the doses reported in the study likely depends on the blood flow that

was achieved. If the blood flow differs, the effective dose may differ. We attempted to illustrate the differences in dose requirements for the two routes by comparing epinephrine dose-responses in the same animal under similar conditions. Increasing the dosage of this powerful vasoconstrictor drug may be a requirement for resuscitation success.

After the circulation is restored, however, high levels of epinephrine may produce dangerous side effects. A period of severe hypertension that was related to the amount of the drug delivered occurred during the recovery period. The duration of the hypertensive episode was greater when epinephrine was given by the ET route and also was dose related. During this hypertensive episode the already compromised heart must work against an increased afterload, causing further damage and perhaps ultimate demise of the subject.

SUMMARY

Our study has shown that ET epinephrine dosage must be much higher than the IV dosage to achieve the same results during resuscitation from electromechanical dissociation. When an effective dosage is given, no difference exists between these routes in the time required to elicit a blood pressure response or in the time to establish circulatory recovery. The hypertension following recovery, however, is both more severe and longer lasting when these higher ET doses are used.

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