Evaluation of Drugs for Cardiac Resuscitation

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In an earlier study, it was shown that intracardiac injection of epinephrine is a valuable adjuvant to artificial ventilation and closed chest cardiac massage during resuscitation from asphyxial arrest. Although the use of epinephrine in this situation was sometimes followed by ventricular fibrillation, external electrical defibrillation usually restored circulation.

The purpose of the present study was to see whether epinephrine contributed to the restoration of circulation in the presence of asphyxia and ventricular fibrillation, and also to determine how effective a number of other drugs might be in asphyxiated animals with cardiac standstill or ventricular fibrillation.

Methods

One hundred and ten mongrel dogs weighing between 6.5 and 11.0 kg were divided into groups of ten. They were lightly anesthetized with sodium pentobarbital, 25 mg/kg, given intravenously, and their tracheas intubated with a cuffed endotracheal tube. A catheter was inserted through a femoral artery into the aorta in order to monitor aortic blood pressure, and lead 2 of the electrocardiogram was recorded continuously.

With each animal secured in the supine position and breathing spontaneously, the endotracheal tube was clamped at the end of an exhalation. From two to four minutes after respiratory efforts became weaker and stopped, the circulation gradually deteriorated with increasing bradycardia and hypotension. From six to eight minutes after airway obstruction all aortic systolic blood pressure fluctuations disappeared. Total circulatory arrest at this point had been confirmed in a series of pilot experiments by cessation of flow in the carotid arteries and by cessation of myocardial activity measured by a Walton-Brodie strain-gauge arch sutured on the left ventricle.

In groups 1 through 7, a period of five minutes was allowed to elapse between circulatory arrest and the start of resuscitation. Then intermittent positive-pressure breathing with room air was begun at a rate of 20 breaths per minute and tidal volumes of 25 ml/kg body weight. Closed-chest cardiac massage was started at the same time with five compressions of the sternum during each exhalation. One minute later one of the following drugs was injected into a cardiac ventricle:

Group 1, epinephrine 1.0 mg; group 2, phenylephrine 10.0 mg; group 3, isoproterenol 0.4 mg; group 4, metaraminol 10.0 mg; group 5, methoxamine 20.0 mg; group 6, naphthylamine 150 mg; and group 7, calcium chloride 200 mg. Artificial ventilation was discontinued at the end of twenty minutes, as was closed-chest cardiac massage unless spontaneous circulation was restored earlier. If ventricular fibrillation appeared during the course of the resuscitation, groups of three 450 volt a.c. shocks each of one-fourth second duration were given to the chest wall.

In groups 8 through 11, a 110 volt a.c. shock was given to the chest wall at the time of circulatory arrest in order to produce ventricular fibrillation. Artificial ventilation and closed-chest cardiac massage, as previously described, were started one minute later. In each animal external electrical defibrillation, as described, was attempted three minutes after resuscitation was started. Drugs were injected into a cardiac ventricle as follows: group 8, no drug; group 9, epinephrine 1.0 mg, after one minute of resuscitation; group 10, phenylephrine 10.0 mg, after one minute of resuscitation; group 11, propranolol 100 mg, just before resuscitation and epinephrine 1.0 mg, one minute later. In each animal artificial ventilation was discontinued after twenty minutes as was closed-chest cardiac

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Results

In asphyxiated dogs with circulatory arrest for five minutes stable 1% epinephrine combined with artificial ventilation and closed chest cardiac massage led to ventricular fibrillation in two animals. External electrical defibrillation was followed by immediate return of circulation in both. All of the animals in group 4 were resuscitated using epinephrine.

Under the same conditions, injection of phenylephrine was followed by ventricular fibrillation in one of the dogs, and external electrical defibrillation was necessary to restore circulation. Nine of the ten dogs in group 2 were resuscitated using phenylephrine (fig. 1).

The injection of isoproterenol was followed by ventricular fibrillation in two of the dogs of group 3 and external countershock effectively restored the electrocardiographic pattern in one of them. However, none of the animals in this group had a return of circulation within the twenty-minute period of resuscitation.

The injection of metaraminol in the ten dogs of group 4 was followed by ventricular fibrillation in one, and this was corrected by external countershock. Nine of the ten dogs were resuscitated.

None of the ten dogs in group 5 had a return of circulation after the injection of methoxamine and ventricular fibrillation did not occur. However, bradycardia and hypotension were noted in conjunction with varying degrees of incomplete heart block.
The use of mephentermine in group 6 was followed by ventricular fibrillation in one animal. In all of the animals increased electrocardiographic activity was noted after injection and occasionally a few weak aortic pulsations were recorded. Three of these ten dogs showed return of an adequate circulation.

In group 7, injection of calcium chloride was followed by ventricular fibrillation on three occasions, and external defibrillation was followed by return of circulation in two of these. An adequate circulation was restored in six of the ten dogs receiving calcium chloride.

In the asphyxiated dogs with ventricular fibrillation (table 2), circulation was effectively restored without the use of drugs in only one of the ten dogs in group 8.

Nine of the ten dogs in group 9, which received epinephrine prior to defibrillation, had a prompt return of circulation. Injection of procaine amide prior to the epinephrine in group 10 was followed by electrical defibrillation and return of circulation in eight dogs.

When phenylephrine was injected prior to defibrillation, circulation returned promptly in all of the animals (fig. 2).

| Table 2. Drug Treatment of Ventricular Fibrillation |
|----------------------------------|---------------|----------------|
| **Group** | **Doses** | **Circulation Restored** |
| 8       | No drug   | 1/10           |
| 9       | Epinephrine, 1.0 mg. | 9/10           |
| 10      | Procaine amide, 100 mg. and Epinephrine, 1.0 mg. | 8/10           |
| 11      | Phenylephrine, 10 mg. | 10/10          |

*Procaine amide was injected into a ventricle one minute after the induction of ventricular fibrillation, at the time closed-chest cardiac massage and ventilation were begun. The other drugs were given one minute after resuscitation was started. External electrical defibrillation was attempted three minutes after resuscitation was started.
Discussion

Since cardiac arrest occurs in the majority of cases because of, or concomitant with, asphyxia we have evaluated these resuscitative measures in a preparation simulating clinical conditions.

The acceptance of closed-chest cardiac massage has focused attention on resuscitation in the wards and outpatient areas where only a few patients have a needle in a vein at the moment of death. Under these circumstances attempts at intravenous medication usually result in considerable loss of time. Intracardiac injection can be performed immediately whenever intravenous injection will cause delay.

Intracardiac epinephrine has often been mentioned as part of the resuscitative armamentarium in cardiac arrest. Failure to follow intracardiac injection by effective cardiac massage probably accounts for many of the failures, and much of the dissatisfaction, that has been associated with this treatment in the past. In addition, the occurrence of ventricular fibrillation must often have been undetected and untreated.

In an earlier publication we reported that, when circulatory arrest due to asphyxia persisted for one minute, only two of ten dogs could be resuscitated by artificial ventilation and closed-chest cardiac massage. When the duration of arrest was increased to five minutes and intracardiac injection of epinephrine was added to the resuscitation procedure, all ten were resuscitated. This clearly indicates the importance of early use of drug therapy in restoration of circulation.

There appears to be no significant difference in effectiveness among the peripheral vasoconstrictors epinephrine, phenylephrine, metaraminol and methoxamine in the dosages used. Figures 1 and 2 show a rise in diastolic pressure during cardiac massage after injection of the pressor substance. It seems likely that these agents work by increasing coronary perfusion during diastole.

Isoproterenol, with a strongly positive inotropic action on the heart and a general peripheral vasodilator effect was of no value in restoring circulation. Phenyldeneurine, with little or no vasoconstrictor activity, was useful in only three of ten dogs in doses as high as 150 mg. The inferiority of phencycloridine compared to epinephrine in the doses used was highly significant ($P < 0.01$).

Calcium chloride was intermediate in effectiveness but significantly inferior to epinephrine ($P < 0.05$) in restoring circulation; ventricular fibrillation followed its use as often as with epinephrine.

The question may be raised whether higher doses of isoproterenol, phencycloridine and calcium chloride would have been more effective. The dose of isoproterenol (0.4 mg.) was based on a cardiac inotropic potency equal to 1 mg. of epinephrine. Phencycloridine in the recommended adult dose of 10 to 60 mg. was without effect. When the dose was increased as high as 150 mg., we achieved only three successful resuscitations, probably due to its secondary effect-peripheral vasodilatation. Since we were interested in its inotropic effect, further increase in dosage would have been misleading. Calcium chloride was given in the dosage commonly used in adults (200 mg.). It is accepted that higher dosage increases the risk of ventricular fibrillation.

The effectiveness of countershock in the correction of ventricular fibrillation is well known but the usefulness of drugs as adjuvants in this situation has not been made clear. The 180 volt shocks given to the twenty dogs in groups 8 and 9 defibrillated nineteen. Circulation was restored in only one of the ten dogs which did not receive drug therapy. Nine of the ten treated with epinephrine had immediate return of circulation. Phencycloridine was as effective as epinephrine under these circumstances.

We often hear that procaine amide is useful in the treatment of ventricular fibrillation. Procaine amide alone did not seem indicated since 9 of 10 dogs were defibrillated when no drug was used, although circulation returned in only one after fifteen minutes of continued massage. When procaine amide and epinephrine were used in combination in group 10 the results were neither better nor worse than when either epinephrine or phencycloridine was used alone. Any benefit from the anti-arrhythmic properties of procaine amide may well be counterbalanced by its myocardial depressant action. Use of procaine amide would appear to be of no advantage in the
treatment of ventricular fibrillation, while the use of one of the vasoconstrictor substances as an adjuvant to ventilation, closed-chest cardiac massage, and external electrical defibrillation is imperative.

Summary and Conclusions

Vasopressor drugs are important adjuvants to artificial ventilation and closed-chest cardiac massage in restoring circulation after circulatory arrest. The peripheral vasoconstrictor agents epinephrine, phenylephrine, metaraminol and methoxamine were of equal value in resuscitation from myocardial standstill. In ventricular fibrillation, epinephrine and phenylephrine are valuable adjuvants in the restoration of circulation by external electrical defibrillation.

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References


PARACERVICAL BLOCK Uterine fundal pain impulses are transmitted through autonomic nerves which pass through the base of the broad ligaments. A blind study of paracervical block of these nerves for pain relief during labor was carried out in 100 cases. The combination of paracervical and pudendal nerve block for delivery gave satisfactory pain relief in 50 per cent of cases. No significant alteration of the course of labor, and no evidence of drug toxicity, infection, hematuria, or serious fetal depression was found. An analgesic during labor, this block was found to be safe and reasonably effective. The major disadvantages were relatively short duration of effect, and limited effectiveness when combined with pudendal block for actual delivery. (Seeds, A. E., B., and others: Paracervical Blocks. Results of a Double-Blind Evaluation, Obstet. Gynec. 20: 162 - Oct.; 1962.

ERGOT The routine administration in the immediate postpartum period of ergonovine maleate resulted in severe headache, nausea, and hypotension in a 17 year old woman. Coma and death followed, owing to intracerebral hemorrhage. The need for ergot derivatives and especially their prophylactic use is questioned. Oxytocin, Pitocin or Synacthen and sparteine sulfate are effective oxytocic agents and are devoid of the presor-inducing effects of ergot derivatives. (Ringrose, C.: The Obstetrical Use of Ergot: A Violation of the Doctrine "Primum Non Nocere." Canad. Med. Ass. J. 87: 712 - Sept. 20; 1962.)