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Influence of Adrenergic Drugs Upon Vital Organ Perfusion During CPR

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Perfusion During CPR

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ABSTRACT

To determine whether adrenergic drugs administered during cardiopulmonary resuscitation (CPR) alter the distribution of artificial cardiac output, we measured regional blood flow and cardiac output using radioactive microspheres in 12 dogs. Ventricular fibrillation was induced electrically and CPR was immediately begun with a mechanical chest compressor and ventilator (Thumper(R)) at 60 compressions/min, with a ventilation:compression ratio of 1:5, a compression duration of 0.5 sec, and a ventilation pressure of 20 cm H_2O. Compression force was sufficient to develop 40-50 mmHg peak intraesophageal pressure. After 30 sec of CPR, either 0.9% saline vehicle or 50 ug/kg of epinephrine, phenylephrine, or isoproterenol was administered through a central venous catheter. One minute later, microspheres were injected into the left ventricle. After 250 sec of CPR the ventricles were defibrillated electrically. Twenty minute recovery periods were interposed between each drug injection. Each dog received all three drugs and saline according to a predetermined sequence. Following saline, epinephrine, phenylephrine, and isoproterenol treatment respectively, cardiac output averaged 392, 319, 255, and 475 ml/min; brain blood flow averaged 37, 54, 29, and 28 ml/min; heart blood flow averaged 25, 79, 26, and 15 ml/min; and kidney blood flow averaged 44, 4, 16, and 29 ml/min. Epinephrine improved blood flow to the brain, probably because of its alpha adrenergic activity. Epinephrine improved blood flow to the heart during

CPR much more than the other agents, probably because of its combined alpha and beta adrenergic activity. This effect may explain its superiority in restoring circulation after prolonged arrest and resuscitation. Isoproterenol should not be used in CPR because it shunts blood away from vital organs.

INTRODUCTION

Epinephrine and other adrenergic drugs are frequently admin-
istered during cardiopulmonary resuscitation (CPR). Putative
beneficial effects of epinephrine in CPR include (1) increased
systemic blood pressure, (2) increased cardiac automaticity, and
(3) diversion of blood to the brain and heart by constriction of
vascular beds in other organs. Also it is commonly held that
epinephrine may make ventricular defibrillation easier by con-
verting fine fibrillation to course fibrillation.

Experimentally, epinephrine increases arterial blood pres-
sure and pulse amplitude when administered during CPR by
intravenous, intracardiac, or intrapulmonic routes (1-5). The
effectiveness of epinephrine appears to result from alpha recep-
tor rather than beta receptor stimulation; since epinephrine and
the alpha agonist, phenylephrine, are almost equally effective in
promoting resuscitation from asphyxia in dogs, whereas the beta
agonist isoproterenol is much less effective (4-5). Yakaitis (6)
and associates have just reported (in this issue) a complimentary
pharmacologic study, showing that animals with beta adrenergic
blockade and control animals are successfully resuscitated from
experimental asphyxia with nearly equal frequency, whereas
animals with alpha adrenergic blockade are not resuscitated as
often as control or beta-blocked subjects.

Presumably, the beneficial action of alpha adrenergic drugs
during CPR is the augmentation of the normal reflex response to

profound hypotension, namely constriction of arterioles to nonessential vascular beds of the skin, kidneys, skeletal muscle, and gut. This causes increased blood flow to the brain and heart because of redistribution of the cardiac output (5). In order to further evaluate the peripheral vascular effects of adrenergic drugs during CPR, we used radioactive microspheres to study the redistribution of cardiac output produced by intravenous injections of epinephrine, phenylephrine, and isoproterenol during ventricular fibrillation with CPR in dogs.

METHODS

Animal Preparation

Twelve mongrel dogs, 6 to 11 kg, of either sex were anesthetized with intravenous sodium pentobarbital (30 mg/kg) and placed in dorsal recumbency on a V-shaped animal board. Intravascular catheters were inserted

(1)   in the left ventricle, via the right femoral artery, for injection of microspheres;

(2)   in the left femoral artery, for withdrawal of blood samples at a known rate to calibrate regional blood flow measurements;

(3)   in the right brachial artery for monitoring systemic arterial blood pressure; and

(4)   in the superior vena cava, via the right maxillary vein,

for monitoring central venous pressure.
Heparin (2 mg/kg) was given to retard clot formation in the catheters and to reduce intravascular coagulation during periods of circulatory arrest.

A Physiograph(R) direct-inking recorder (Narco Bio-Systems, Houston, Texas) displayed the electrocardiogram (Lead II) and the arterial and venous blood pressures. To monitor the intrathoracic pressure generated by chest compression, a water filled soft rubber tube, 25 cm long and 1 cm in diameter, was placed in the esophagus between the thoracic inlet and the diaphragm and connected to a pressure transducer.

Measurement of Regional Blood Flow

Radioactively labelled polystyrene microspheres (3M CO., Minneapolis, Minn) with a diameter of 15±3 microns were used to measure regional and total blood flow according to the method reviewed by Heymann[7]. Microspheres containing four different gamma-emitting labels (^{141}Ce, ^{85}Sr, ^{95}Nb, ^{46}Sc) were employed. A different label was used with each adrenergic drug tested. The microspheres were suspended in a 10% dextran solution. One minute following administration of each test drug during CPR, 1.0 ml of well-mixed suspension containing approximately 5×10^5 microspheres was injected into the left ventricle and the catheter was flushed with 10 ml of 0.9% saline. This technique produces adequate mixing of the microsphere suspension with blood in the left ventricular chamber during fibrillation with CPR [8].

A "surrogate organ" reference blood sample was collected from the femoral artery at a known rate of 7.5 ml/min, starting 10 sec before the microsphere injection and continuing for 120 sec. Passage of the microspheres into the periphery could be inferred by monitoring the electrictal impedance of blood passing into the motor driven syringe through a 0.1 ml volume conductivity cell. Return of blood impedance to the preinjection baseline indicated passage of the diluted microsphere suspension into the femoral artery and gave evidence that the injected microspheres had been distributed to peripheral organs. Then the ventricles were defibrillated, typically after a total of 250 seconds of CPR. Following each experiment, tissue samples and the "surrogate organ" blood sample were counted in a Beckman 8000 gamma-counter (Beckman Instruments, Inc, Fullerton, CA). Total flow (cardiac output) was calculated from the measured counts per minute (CPM) according to the relationship:

$$\frac{\text{Total Flow}}{\text{CPM Injected}} = \frac{\text{Surrogate Organ Flow}}{\text{Surrogate Organ CPM}} \; .$$

Regional blood flow to the tissue samples was calculated according to the relationship:

$$\frac{\text{Tissue Flow}}{\text{Tissue CPM}} = \frac{\text{Surrogate Organ Flow}}{\text{Surrogate Organ CPM}} \ .$$

CPR Technique

We employed the ventricular fibrillation model of cardiac arrest rather than the asphyxia model of Redding and Pearson (4) because the fibrillation model permits repeated trials of resuscitation in the same animal. Ventricular fibrillation was induced by a train of 60-Hz, square-wave electrical stimuli. The stimuli were delivered via a stainless steel wire (0.1 mm diameter) in the lumen of the left ventricular catheter. CPR was performed using a mechanical chest compressor and ventilator (Thumper(R), Michigan Instruments, Inc., Grand Rapids, MI). Minor modifications were made to adapt this device for use on a dog. A 6 by 10 cm compression pad was centered on the midline of the chest with its caudal edge at the level of the xiphi-sternal junction. The pad was covered with a wire mesh defibrillation electrode. Compression force was adjusted to maintain peak intraesophageal pressure of 40-50 mm Hg. CPR was performed at 60 compressions/min, with compression duration equal to 50% of the cycle length (50% duty cycle), and ventilations were interposed after every fifth chest compression. Peak inspiratory pressure was 20 cm H_2O. The oxygen concentration of inspired gas was approximately 80%. Defibrillation was accomplished at the time of a chest compression with a damped sinusoidal current pulse

(20-50 joules) applied between a V-shaped electrode under the animal and the wire mesh of the compression pad, both of which had been covered with a low resistivity electrode gel.

Experimental Design

The protocol for each dog consisted of four sequential fibrillation/CPR-defibrillation episodes, separated by 20 minute recovery periods. In each episode, CPR was initiated immediately following the induction of ventricular fibrillation. After 30 sec of CPR, either 0.9% saline vehicle (SAL) or 50 ug/kg of epinephrine (EPI), phenylephrine (PE), or isoproterenol (ISO) was administered through the central venous catheter. Each dog received all three drugs and saline according to a predetermined sequence (Table 1). Hence each animal served as its own control. A different drug sequence was chosen in each of 4 subgroups to balance potential effects of the order of drug administration. One minute after drug administration, microspheres labeled with one of the four radionuclides were injected rapidly into the left ventricle. CPR continued until passage of microspheres into the surrogate organ was confirmed by the impedance detector. During the 20 minute recovery period after each episode, the volume of blood withdrawn into the "surrogate organ" was replaced with 0.9% saline, the blood pressure was allowed to stabilize, and the dogs were weaned from the ventilator to spontaneous breathing of room air.

Following recovery from the final episode, each dog was

euthanized by an overdose of barbiturate. The brain, heart, and kidneys were excised, sectioned, weighed, and their radioactivity measured. Cardiac output and regional blood flows were calculated, and mean arterial blood pressure during each resuscitation was tabulated from the graphic records. Using Student's t-test for paired observations at a significance level of $p = 0.05$, we tested the null hypothesis that cardiac output, blood pressure, and regional blood flows were the same following each drug treatment as compared to saline treatment.

RESULTS

Figures 1a-1c show the effects of drug treatment on cardiac output, arterial blood pressure, and arteriovenous pressure difference. Compared to saline treated controls, epinephrine treated animals exhibited significantly higher arterial pressure and arteriovenous pressure difference. The pure vasoconstrictor, phenylephrine, produced a significant decrease in cardiac output. Cardiac outputs, regional blood flows, mean arterial pressures, and mean arteriovenous pressure differences during CPR did not vary significantly with the sequence of drug administration nor with the trial number.

Epinephrine produced a theoretically desirable redistribution of cardiac output during CPR, enhancing blood flow to the heart and brain (Figure 2(a)). The increase to brain is remarkable because blood flow to the brain (Figure 2(b)) does not decrease during CPR in this animal model (8). Epinephrine

profoundly decreased blood flow to the kidneys (Figure 2(c)). Although phenylephrine also restricted flow to the kidneys, it did not improve flow to the brain or heart compared to saline treated controls. Blood flows to the heart and brain were less with isoproterenol, even though total cardiac output did not decrease.

DISCUSSION

These data confirm the basic tenet of Redding's hypothesis that the peripheral vascular effects of adrenergic drugs redirect the available blood flow to the heart and brain during CPR (5). The vasoconstrictive effect of alpha adrenergic agonists are probably important in this regard. However, we found that the pure alpha agonist and vasoconstrictor, phenylephrine, decreased cardiac output and tended to raise blood pressure without improving coronary or cerebral flow. The greatest increase in coronary perfusion occurred with the combined alpha and beta adrenergic stimulation of epinephrine, presumably because of both the increased perfusion pressure due to generalized peripheral vasoconstriction and the relative coronary vasodilation caused by stimulation of beta receptors.

We conclude that epinephrine is still the drug of choice for producing a favorable redistribution of cardiac output during CPR. Its mechanism of action depends upon both alpha and beta adrenergic activity. Isoproterenol alone should not be used in CPR because it shunts blood away from vital organs.

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FIGURE LEGENDS

Figure 1: Hemodynamic variables following adrenergic drugs during CPR. Each data point represents the mean value for 12 dogs ± Standard Error of the Mean (S.E.M.). * indicates a significantly different effect than saline (SAL).

Figure 2: Regional blood flows following adrenergic drugs during CPR. Each data point represents the mean flow per kilogram body weight ± S.E.M. * indicates a significantly different effect than saline (SAL).

Table 1: Balanced sequences of drug
administration in 4 groups
of 4 dogs each.

GROUP	DRUG SEQUENCE			
1	SAL	EPI	PE	ISO
2	EPI	SAL	ISO	PE
3	PE	ISO	SAL	EPI
4	ISO	PE	EPI	SAL

Fig. 1a

Fig 18

MEAN ARTERIAL PRESSURE (mmHg)

SAL   EPI   PE   ISO

Fig. 1c

A-V PRESSURE DIFFERENCE (mmHg)

SAL   EPI   PE   ISO

Fig. 2a

Fig. 26

BRAIN FLOW (ml/min/kg)

SAL   EPI   PE   ISO

Fig. 20

KIDNEY FLOW (ml/min/kg)

SAL   EPI   PE   ISO