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THE EFFECTS OF CATECHOLAMINES ON HEMORRHAGIC SHOCK IN DOGS

By

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ABSTRACT

The effects of isoproterenol, dopamine, dobutamine and the combination of dopamine and dobutamine were compared by using forty-two mongrel dogs in hemorrhagic shock states. The combined use of dopamine and dobutamine was considered to be the most effective in the treatment of hemorrhagic shock in view of the small increase in heart rate, the large and steady increase in cardiac output, the maintenance in renal arterial blood flow and the mild increase in peripheral resistance.

INTRODUCTION

Pathophysiology of a shock state has been progressively elucidated. In the early times, improvement of arterial blood pressure was the main treatment of shock, but at the present time, various measures are performed, such as the improvement of blood flow in the visceral organs, the recovery of cellular functions, the normalization of metabolism and so on. However, it is needless to say that the improvement of both the cardiac function and blood flow in the visceral organs (especially in the kindney) is the most fundamental to cure the shock state. Various kinds of drugs are used in order to perform these measures. In many cases, sympathomimetic amines that increase the cardiac output and blood flow are indispensable. Therefore, in this study, isoproterenol, dopamine and dobutamine were chosen and the hemodynamic effects of these drugs on hemorrhagic shock in the dogs were investigated.

METHODS

Forty-two mongrel dogs were anesthetized with 20 mg/kg of secobarbital sodium and intubated with succinylcholine chloride. Ventilation was kept with 100% oxygen to adjust the $PaCO_2$ within the normal range by a volume-preset ventilator. Catheters were inserted into the right femoral artery and the left femoral vein. Ten ml/kg/hour of Ringer's lactate solution were infused until the end of the experiment. After splenectomy, electromagnetic flow probes were fixed to the left renal artery, the left femoral artery and the ascending aorta. After these surgical performances, the heart rate (H.R), mean arterial blood pressure (MAP), ascending aortic blood flow (C.O), renal arterial blood flow (RBF), femoral arterial blood (FBF), blood gas and central venous pressure were measured (pre-hemorrhagic data). Then the arterial blood was drawn from the right femoral artery until the

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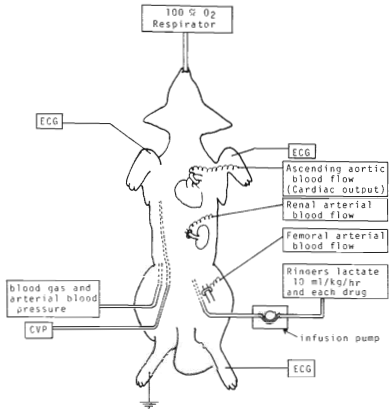

Fig. 1. Schema of the Experiment.

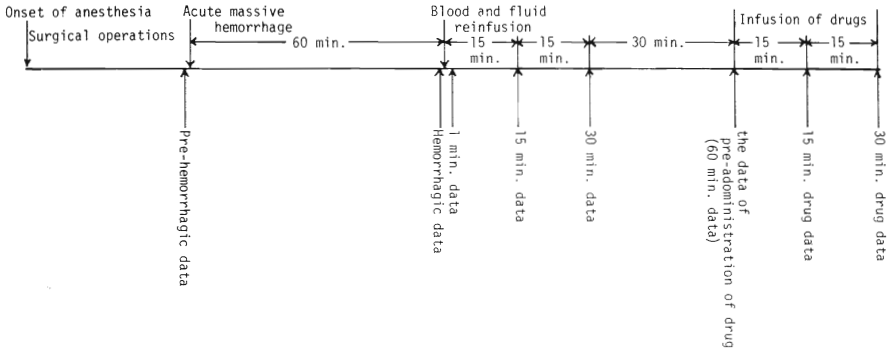

Fig. 2. Time Schedule of Experiment.

Table 1. Seven Groups and Their Infused Drugs and Infusion Rate

	Infused drugs and their infusion rates	
I	Ringer's lactate solution 10 ml/kg/hr only (the non-treated group)	
II	(I)+Isoproterenol 0.1 μg/kg/min	(Isp group)
III	(I)+Dopamine 5 μg/kg/min	(DOA 5 μg group)
IV	(I)+Dopamine 10 μg/kg/min	(DOA 10 μg group)
V	(I)+Dobutamine 5 μg kg min	(DOB 5 μg group)
VI	(I)+Dobutamine 10 μg/kg min	(DOB 10 μg group)
VII	(I)+Dopamine 5 μg/kg/min +Dobutamine 10 μg kg/min	(the combined group)

MAP fell to 40 torrs. The MAP was maintained at this level for 60 minutes in order to cause a hemorrhagic shock; thereupon hemodynamic measurements were performed at the shock level (hemorrhagic data).

And the blood and the same volume of Ringer's lactate solution were reinfused rapidly from the vein. Each parameter was measured 1, 15, 30 and 60 minutes

after the reinfusion. Dogs were divided into seven groups and each drug was given for 30 minutes (Table 1). Parameters were measured at the points of 15 minutes and 30 minutes after the drug was infused. The time schedule and the schema of this experiment are shown in Fig. 1 and Fig. 2, respectively.

Results

I. Hemodynamic effects of blood and fluid reinfusion

Hemodynamic parameters which had been aggravated by massive bleeding returned nearly to the pre-hemorrhagic level except for the H.R and peripheral resistance (TPR) (Table 2). Especially the C.O and FBF increased to 182.4±87.6% and 161.6±94.6% of the pre-hemorrhagic values, respectively. However, the hemodynamic effects of the reinfusion were transient, especially the C.O, RBF and FBF.

II. Hemodynamic effects of drugs

In this section, to analyze the effects of the drugs, 15-minute and 30-minute drug data were compared with the pre-administration data (60-minute data). And besides, the statistical significance between the effect of the non-treated group and that of the drug groups was determined by the paired t test. H.R increased to 124.2±19.7% (15 min) in the Isp group, 120.0±12.5% (15 min) and 119.7±12.2% (30 min) in the DOB 5 μg group, and 134.4±21.8% (15 min) and 133.9±17.5% (30 min) in the DOB 10 μg group (Fig. 3, Table 3). The Isp group and DOB groups showed a significant increase in comparison with the non-treated group. MAP was reduced to 91.9±7.5% (30 min) in the non-treated group and 77.6±20.4% (15 min) and 74.6±13.7% (30 min) in the Isp group, but increased to 118.9±14.1% (30 min) in the DOA 5 μg group, 118.1±16.2% (15 min) and 124.9±22.9% (30 min) in the DOA 10 μg group, and 135.7±28.8% (15 min) and 136.4±26.3% (30 min) in the combined

Table 2. Hemodynamic Effects of Blood and Fluid Reinfusion

	Pre-hemorrhagic data	hemorrhagic data	1 min. data	15 min. data	30 min. data	60 min. data
H.R	100	95.4±17.6	84.5±15.5**	83.0±11.1**	83.4±11.8**	83.5±13.9**
MAP	100	42.2±12.4**	97.5±21.2	103.7±19.1	101.1±19.8	93.9±21.3
C.O	100	53.5±17.6**	182.4±87.6**	137.2±67.2**	108.1±44.9 (n=41)	97.9±40.7
RBF	100	46.1±23.0**	102.5±43.6	98.7±55.8	91.3±35.0	81.3±26.1**
FBF	100	45.4±33.4** (n=41)	161.6±94.6** (n=41)	133.5±72.3** (n=40)	111.3±51.8 (n=41)	98.5±44.5 (n=41)
RFR	100	93.5±48.9	81.5±91.3	90.2±63.4	107.7±90.8 (n=41)	103.8±79.7
FFR	100	86.8±57.8 (n=41)	101.6±60.9 (n=41)	112.1±59.9 (n=40)	120.8±69.8 (n=40)	114.9±62.9 (n=41)
TPR	100	86.7±36.3*	66.4±32.4**	92.7±41.1	108.7±47.9	108.0±39.7

H.R: Heart rate, MAP: Mean arterial blood pressure, C.O: Cardiac output, RBF: Renal arterial blood flow, FBF: Femoral arterial blood flow, RFR: Renal fraction rate of cardiac output, FFR: Femoral fraction rate of cardiac output, TPR: Total peripheral resistance
Values=mean±SD *: statistic significant $P<0.05$ **: statistic significant $P<0.01$

Table 3. Hemodynamic Effects of Drugs

		H.R	MAP	C.O	RBF	FBF	RFR	FFR	TPR
60-minute data		100	100	100	100	100	100	100	100
15-minute drug data	the non-treated group	100.8± 4.0	92.9± 9.6	87.5±10.1*	93.2± 4.3*	93.2± 21.7	107.7±13.2	104.6±15.9	107.7±18.3
	Isp group	124.2±19.7*	77.6±20.4*	104.4±25.3	117.2±39.1	120.4± 52.8	117.2±43.1	112.8±30.9	81.7±42.2
	DOA 5 μg group	101.9± 9.6	110.7±12.2	101.8± 7.1	129.5±11.8**	99.0± 11.1	128.7±15.8**	99.3± 5.3	109.4±16.2
	DOA 10 μg group	102.2±24.7	118.1±16.2*	107.3±36.0	135.8±15.1**	104.8± 48.6	146.1±78.6	111.6±44.3	120.9±47.3
	DOB 5 μg group	120.0±12.5*	108.2±14.8	111.5±19.7	102.7±33.5	106.0± 30.3	94.8±29.7	97.7±33.8	98.3±13.2
	DOB 10 μg group	134.4±21.8**	106.5±15.0	132.8±51.8	101.2±14.3	94.9± 15.0	83.6±21.6	77.0±21.5*	87.1±22.5
	the combined group	114.9±16.8	135.7±28.8*	130.1±28.7	125.0±37.1	140.2± 32.2*	101.7±44.6	111.3±28.0	111.3±21.5
30-minute drug data	the non-treated group	98.3± 5.0	91.9± 7.5*	79.3±22.3	83.1±12.8*	79.5± 27.0	109.7±27.9	100.0±19.9	122.5±28.6
	Isp group	127.4±31.2	74.6±13.7**	109.1±17.6	117.6±46.9	145.5±105.3	110.4±41.9	128.5±77.8	76.1±29.9
	DOA 5 μg group	97.1±15.5	118.9±14.1*	103.4±15.1	133.5±15.0**	101.7± 35.6	131.8±16.8**	102.0±36.0	116.4±17.4
	DOA 10 μg group	112.8±23.6	124.9±22.9*	101.3±33.9	139.1±25.5*	114.4± 41.5	157.2±82.1	133.5±58.0	131.0±36.8
	DOB 5 μg group	119.7±12.2*	105.6±21.2	109.9±28.7	95.9±18.9	111.2± 22.9	94.9±30.0	101.9±17.8	98.6±22.0
	DOB 10 μg group	133.9±17.5**	107.3±30.4	151.1±65.1	106.9±22.1	87.9± 14.3	79.0±23.8	64.7±18.3**	78.2±25.0
	the combined group	115.5±20.1	136.4±26.3*	121.1±18.3*	124.1±36.4	123.6± 23.7	105.2±38.8	103.9±18.9	114.1±22.9

H.R: Heart rate, MAP: Mean arterial blood pressure, C.O: Cardiac output, RBF: Renal arterial blood flow, FBF: Frmoral arterial blood flows, RFR: Renal fraction rate of cardiac output, FFR: Femoral fraction rate of cardiac output, TPR: Total peripheral resistance
Values=mean±SD *: statistic significant $P<0.05$ **: statistic significant $P<0.01$

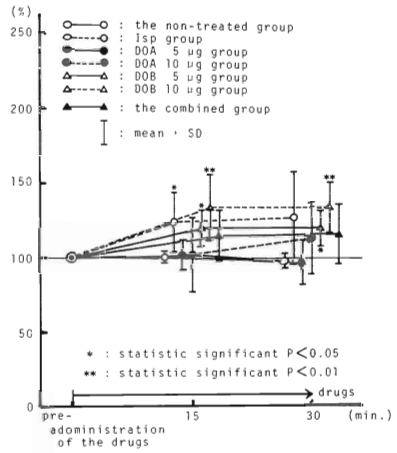

Fig. 3. Percent Changes in Heart Rate.

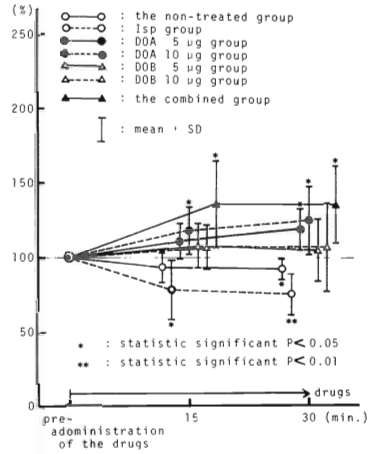

Fig. 4. Percent Changes in Mean Arterial Blood Pressure.

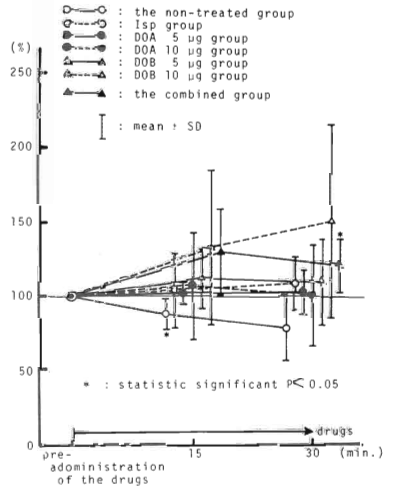

Fig. 5. Percent Changes in Cardiac Output.

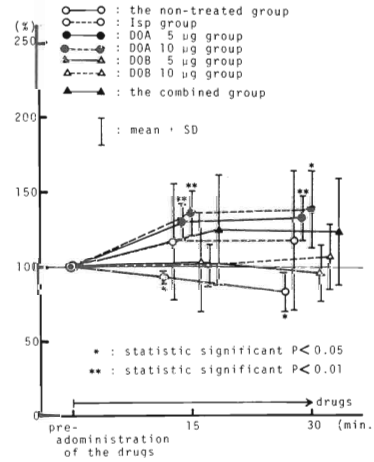

Fig. 6. Percent changes in Renal Arterial Blood Flow.

group (Fig. 4, Table 4). Comparing the drug groups with the non-treated group, there was a significant decrease of MAP in the Isp group and a significant increase in the DOA groups and the combined group. C.O decreased to 87.5±10.1% (15 min) in the non-treated group. It increased to 121.1±18.3% (30 min) in the combined group (Fig. 5, Table 3). Comparing the drug groups with the non-treated group, C.O of the Isp group, DOB 10 μg group and the combined group increased significantly. RBF decreased to 93.2±4.3% (15 min) and 83.1±12.8% (30 min) in the non-treated group. However, it increased to 129.5±11.8% (15 min) and 133.5±15.0% (30 min) in the DOA 5 μg group, and 135.8±15.1% (15 min) and 139.1±25.5% (30 min) in the DOA 10 μg group (Fig. 6, Table 3). Comparing the drug groups with the non-treated group, RBF of the DOA groups, DOB 10 μg group and the combined group showed a significant increase. FBF increased to 140.2±

32.2% (15 min) in the combined group and the other groups did not show a change from the control (Table 3). Comparing with the non-treated group, FBF of the combined group showed only a significant increase. The renal fraction rate of C.O increased to 128.7±15.8% (15 min) and 131.8±16.8% (30 min) in the DOA 5 μg group (Table 3). Compared with the non-treated group, the fraction rate of the DOA 5 μg group showed a significant increase and that of the DOB 10 μg group showed a significant decrease at the 15-minute point. The femoral fraction rate of C.O decreased to 77.0±21.5% (15 min) and 64.7±18.3% (30 min) in the DOB 10 μg group (Table 3). In comparison with the non-treated group, the fraction rate of only the DOB 10 μg group showed a significant decrease. In no group did TPR (total peripheral resistance) show a significant change from the control (Table 3). Comparing with the non-treated group, TPR of the Isp group and the DOB 10 μg group showed a significant decrease.

Discussion

When blood and fluid reinfusion was performed after a hemorrhagic shock state which had been caused by acute massive bleeding, the hemodynamic data showed a recovery to the pre-hemorrhagic state. But the restoration was transient and the hemodynamic parameters were aggravated gradually. And then at the 60-minute point these parameters took a turn for the worse in comparison with the values of the one-minute data. If no treatment were instituted at this point, it was clear that the subjects would have fallen again into the shock state. C.O, MAP, RBF and FBF decreased significantly or had a tendency to decrease in the non-treated group. On the other hand, the hemodynamic changes by the administration of three kinds of drugs are described under the section on results. In this study, the utility and the indication of these drugs are discussed on the basis of the results and previous reports.

A. Isoproterenol

Isoproterenol is said to have a positive chronotropic and inotropic effect, but is also reported that it decreases the peripheral resistance (especially that of the muscle and skin) and reduces the MAP when the circulatory blood volume is insufficient (Daniell et al. (1); Dodge et al. (2); Loeb et al. (3); Mueller et al. (4); Rosenblum et al. (5); Silberschmid et al. (6); Smith et al. (7)). Comparing with the non-treated group, in the Isp group isoproterenol increased the H. R and C.O but reduced the MAP further because of the decrease in the TPR in our study. It was reported that isoproterenol didn't change the RBF (Rosenblum et al. (5); McNay et al. (8)) and DiSalvo et al. (9) attributed the reason for this to the absence of the β-receptor in the renal vascular smooth muscle. In our experiment, isoproterenol didn't change the RBF and the renal fraction rate of C.O. It is also said that isoproterenol increases the FBF (blood flow in the muscle and skin) (Rosenblum et al. (5); McNay et al. (8)) but this effect was not apparent in this study.

B. Dopamine

There are many reports which state that dopamine has a positive inotropic effect and its influence on the perpheral vessels depended on the infused dose (Goldberg (10), Goldberg et al. (11)); namely at infusion rate of 5 μg/kg/min or less, the peripheral resistance decreased or changed little but, at a higher infusion rate, the α-effect of dopamine becomes apparent in the peripheral vessels. But in our study, the peripheral resistance showed a tendency to increase as compared to the control value and the difference from the non-treated group in both DOA groups was

small. The result indicates that dopamine at these infusion rates has no evidence of α-stimulation. On the other hand, there were significant differences in the MAP as compared to the control and the non-treated group, because of the constantly maintained C.O.

The effect of dopamine on the renal vessels is unique. Dopamine acts directly and increases the RBF (Rosenblum et al. (5); McNay et al. (8); Goldberg (10); Goldberg et al. (11); Higgins et al. (12)). Nagakawa et al. (13) reported that dopamine increased the cortical perfusion markedly and dilatated particularly the afferent arterioles in the kidney. But, McDonald et al. (14) reported that dopamine didn't increase significantly the renal fraction rate of C.O in the normal man, and Gifford et al. (15) said that RBF increased significantly by dopamine during the experimental hemorrhagic shock in dogs but that the changes in the renal fraction rate was not statistically significant. Concerning the effects on the renal vessels, two different observations were reported: (1) Dopamine had a particular effect on the RBF and also changed the intrarenal distribution of the renal blood flow. (2) Dopamine increased the RBF too but had no effect on the change in the renal fraction rate of C.O.

RBF increased significantly by the infusion of dopamine, and the renal fraction rate increased significantly at the infusion rate of 5 μg/kg/min and showed a tendency to increase at the infusion rate of 10 μg/kg/min in our dog experiment (Fig. 6, Table 3). At the infusion rate of 5 μg/kg/min dopamine must change the fraction rate of C.O and increase particularly the RBF though the intrarenal changes are unknown.

Dopamine is widely used in the treatment of various shocks, but caution is necessary in using it clinically because of the occurrence of gangrene in the extremities (Alexander et al. (16); Greene et al. (17)) and vasoconstriction by intra-arterial injection (McNay et al. (8)).

C. Dobutamine

There are many reports which state that dobutamine has little chronotropic effect (Andy et al. (18); Gillespie et al. (19); Stoner et al. (20) Tuttle et al. (21)). However, Robie et al. (22) noted that dobutamine produced a dose-related chronotropic effect. Loeb et al. (23) stated that it increased the sinus node automaticity and enhanced the A-V nodal conduction, and Bianchi et al. (24) indicated that dobutamine was effective when there was a disturbance in the A-V nodal conduction. And our result was agreeable with Robie's reports. Considering these results, a positive chronotropic effect of dobutamine can't be denyed. According to Tuttle et al's report (25), dobutamine increases the cardiac contractility and increases the C.O. Furthermore, it reduces the TPR and has an advantage of decreasing the after-load to the heart. The infusion rate of dobutamine 10 μg/kg/min showed results which were similar to the other reports (Andy et al. (18); Robie et al. (22); Tuttle et al. (25); Tinker et al. (26)). Dobutamine 5 μg/kg/min was able to keep both the C.O and TPR at the level of the control. It was also reported that dobutamine had little effect on the renal vessels and so decreased the renal fraction rate of the C.O (Robie et al. (22); Vatner et al. (27)). Dobutamine 10 μg/kg/min had a tendency to decrease the renal fraction rate of C.O but RBF could be improved by the increase in C.O. In FBF, a significant change was not obtained but the femoral fraction rate of C.O decreased significantly in the DOB 10 μg group. So, in this study, dobutamine didn't increase the blood flow to the muscle and skin. Our results differed from the reports by Vatner (27) and Robie

(22).

D. Combined use of dopamine and dobutamine

When dopamine and dobutamine were used in combination, H.R showed nearly a value midway between the DOA 5 μg group and the DOB 10 μg group. This phenomenon is considered to be a state where dopamine negates the positive chronotropic effect of dobutamine. The reason is unknown why dopamine, which has no negative chronotropic effect, shows a suppressive effect by the additional use of dobutamine. C.O increased by the combined usage but the increase was smaller than that in the DOB 10 μg group and its standard deviation was smaller than one-third of that in the DOB 10 μg group. This phenomenon suggests that cases ineffective by dobutamine is reduced by combining with dopamine though the increase becomes smaller and that it is valuable clinically. TPR changed more similarly to that of the DOA 5 μg group. MAP increased the greatest because the TPR didn't decrease but the C.O increased. Both in the RBF and in the renal fraction rate of C.O, the mean values were located between that of the DOA 5 μg group and the DOB 10 μg group. There were similar results with the H.R and C.O. So, the specific effect of dopamine on the kidney suppressed by dobutamine.

E. Utility and clinical indication

Three kinds of catecholamines were investigated in the hemorrhagic shock dogs. Isoproterenol reduced the TPR which was an advantage from the point of the improvement of the peripheral circulation and the reduction of the after-load, but was a disadvantage in not maintaining the perfusion pressure in the important visceral organs, because isoproterenol decreased the MAP. Considering these facts and because of tachycardia, isoproterenol may not be competent for the management of hemorrhagic shock. But it has some indications for the patient with conducting disturbance.

Dopamine changes the heart rate a little at a infusion rate of 5~10 μg/kg/min. In spite of the mild inotropic effect, it increases the RBF selectively and keeps the perfusion pressure in importent visceral organs. Therefore, dopamine is suitable for application in hemorrhagic shock where myocardial injury is slight.

Dobutamine is similar to isoproterenol on the point of decreasing the TPR and increasing the C.O. But it is more appropriate for hemorrhagic shock than isoproterenol in the respect that dobutamine is able to retain the perfusion pressure in the important visceral organs. Superiority of dobutamine over isoproterenol and dopamine is reported in the cases of cardiogenic shock or congestive heart failure by many investigators (Stoner et al. (20); Leier et al. (28); Loeb et al. (29); Sakamoto et al. (30)). But dopamine may be a good choice in hemorrhagic shock because of its surpassing effect on the renal vessels.

The advantages of the combined use of dopamine and dobutamine are recognized by the changes in the H.R and C.O. But the combination negates the advantage of one over the other in regard to the RBF and TPR. However, the combined use may be considered to be most effective in the treatment of hemorrhagic shock from the point of the small rise in H.R, the large and steady increase in C.O, the maintenance of the RBF level and the mild increase in TPR.

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